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INVESTIGATIONS ON A PATIENT SUBJECT TO MYOCLONIC SEIZURES AFTER SENSORY STIMULATION

BY

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(RECEIVED 29TH NOVEMBER, 1947)

Introduction

THE discharges which occur in the electroencephalogram (EEG) during myoclonic seizures have been described by Grinker, Serota, and Stein (1938), by Gibbs and Gibbs (1941), and by Jasper (1941a). None of these workers reported any effects of sensory stimulation on the course of the seizures or on the characters of the disturbances in the EEG. Two patients have been described (Dawson, 1946) in whom sensory stimulation under favourable conditions would provoke a myoclonic seizure. During the seizure which followed a stimulus such as a tap on a tendon, the discharges in the EEG seemed to be larger on the side of the head opposite to the limb stimulated. The evidence that this difference in the size of the discharge on the two sides of the head was related to the side of the body stimulated was not considered to be satisfactory. The purpose of this paper is to describe experiments carried out on a single subject in whom sensory stimuli provoke myoclonic seizures. These seizures are preceded by electrical disturbances which are detectable on the scalp and whose characters suggest that they are of cerebral origin. The disturbances appear largest on the side opposite to that stimulated; they appear near to the midline when the stimulus is applied to a leg and more laterally when it is applied to an arm. Studies have been made of the characters of these discharges and of the afferent systems concerned in their production.

Material

The patient, who was demonstrated at a clinical meeting (Carmichael, 1947), is a male, aged 42 years, with no family history of epilepsy or nervous disorder and no relevant past medical history. He attended the out-patient clinic for the first time in May, 1945, with the complaint that for eight months past when he put his weight on to his toes, or tried to climb a ladder, he had a feeling of uncertainty and later his feet began to shake. Also he had on several occasions fallen to the ground, but had been able to rise again immediately. There was no loss of consciousness or incontinence on these occasions. On one later occasion, just prior to admission, he had lost consciousness and bitten his tongue. Examination showed nothing but a suggestion of pyramidal dysfunction on the left side and he was admitted for fuller investigation in June, 1945.

After admission nothing abnormal was detected in the nervous system, in the cerebrospinal fluid, or in the skull by radiograph. An air encephalogram showed no abnormality. Dr. Hill reported that an EEG showed some abnormally slow rhythms in both parietal regions which were sometimes rather greater on the left than on the right side. These rhythms had a frequency of 4 to 7 c/s. and they were augmented by overbreathing in the fasting state but not after the administration of 50 g. of glucose by mouth. This finding was interpreted as being evidence against a diagnosis of idiopathic epilepsy, but there was no positive evidence of any localized abnormality or of an expanding lesion. Later during his stay in hospital the patient had two convulsive seizures in which the initial symptom was a drawing up of the legs. In these attacks consciousness was lost, he bit his tongue, and there was incontinence of urine. Treatment was started with phenytoin and phenobarbitone and he was discharged.

During the following eighteen months the patient became subject to severe myoclonic jerkings on which was superimposed, whenever he tried to walk, a bizarre rigidity in extension of the limbs and trunk. His rather cheerful indifference to his symptoms led to a diagnosis of hysteria.

In February, 1946, eighteen months after the onset of the illness, he was readmitted for further investigation, which again showed no evidence of any lesion that might be causing his symptoms. At

this time the jerkings appeared locally, in which case they were almost invariably found in the muscles producing extension of the right big toe, or generally, affecting both legs and spreading to the arms, face, and diaphragm. During the less localized jerks the limbs became fixed for a period of half a second or less in an attitude between extension and flexion ; they did not show the great predominance of flexion that was characteristic of the two patients with myoclonus previously described (Dawson, 1946). The jerks occurred singly or in groups of diminishing severity separated by intervals of about a second or less. Examination of the reflexes was complicated by the fact that a tap on a tendon was usually followed by a generalized jerking whether the stimulus was applied to an arm or to a leg. Similar jerkings were produced by any sudden active or passive movement or by any stimulus to the patient such as a jar applied to the bed. Extensive sensory tests made by Dr. Norton showed that the only stimulus adequate for producing a myoclonic spasm was stretching of a muscle. Light touch, pinprick, heat and cold, or pressure, failed to cause any jerking so long as the stimulus was applied in a manner avoiding movement of a muscle. The threshold to stimulation was highest immediately after a previous jerk had occurred, and was then found to become progressively lower until finally a jerk would occur without any stimulus being applied, apparently spontaneously. The spontaneous jerkings occurred at intervals varying from a few minutes to a quarter of an hour, the frequency altering from day to day and remaining higher during periods of wakefulness than during sleep. On some occasions the jerkings seemed to be more frequent when the patient was starving, but raising the blood sugar did not prevent them and no abnormality was found in his tolerance to sugar. Increasing doses of phenytoin and phenobarbitone up to toxic levels made the jerkings worse, and when the drugs were withheld there was a considerable improvement in the patient's condition. Following this, amphetamine, 5 mg. three times a day, was given, and this resulted in a striking temporary improvement which was not, however, maintained.

The patient's condition remained stationary up to September, 1946, when he had a major convulsive seizure, the second since his readmission to hospital seven months before. This seizure began with a sensation of numbness which spread upwards from the left hand to the middle of the upper arm before consciousness was lost, This onset showed a change from that in earlier attacks, in which the initial symptoms were in the feet, especially the toes of the right foot. From that time the patient's condition has deteriorated slowly but steadily, with some remissions which have taken place particularly after major convulsions. The frequency of major seizures is now about three a month, with one free month in March, 1947, and one group of eleven seizures in twenty-four hours in May, 1947. Now he is quite unable to move without the occurrence of severe myoclonic jerkings which make articulation impossible. Between the more massive jerkings which occur almost continuously throughout the day and less frequently at night, there are coarse twitchings of groups of muscles all over the body and the plantar responses are now clearly extensor on both sides. The condition has been alleviated but not controlled by the administration of bromides. During the last five months the left hand and arm have become spastic and contracted in a slightly flexed posture, but are still involved in the jerkings. Apart from severe wasting the patient's general condition remains unchanged. No further laboratory tests have revealed any abnormality except the electrical investigations, the results of which are to be described. The cause of the condition remains obscure.

Methods

In these studies the differences of electric potential on the scalp were recorded by three different methods. For those experiments in which records over long periods were needed and when accuracy of recorded waveform was not of primary importance, ink-writing oscillographs were used. With the exception that the electrodes used were silver cups, coated with silver chloride and fixed to the scalp with collodion, the technique used was the same as that described previously for work on patients with myoclonus (Dawson, 1946). When accuracy of the recorded waveform was important the inkwriters were replaced by cathode ray oscillographs and the record was made on continuously moving bromide paper. To indicate the time at which stimulation with a tendon hammer was applied it was arranged that the contact of the hammer with the skin discharged a small condenser through the subject, producing a brief deflection in the record. This deflection indicated a time slightly earlier than that at which the actual sensory stimulation occurred and for greater accuracy of timing an electric shock applied to peripheral nerve was used as the stimulus. The third method of recording used was that described for studies of the cerebral responses to sensory stimulation in healthy subjects (Dawson, 1947), where the methods for electrical stimulation have also been described. With this method of recording a number of records of the responses to stimulation are superimposed in such a way that the artefacts in the records due to the stimuli coincide. Any features of the responses occurring regularly after the stimuli tend to superimpose and are emphasized, whilst irregularities in the records unrelated to the stimuli become less prominent. The difficulties of timing the start of a response are thus greatly reduced. All records read from left to right and the values of the

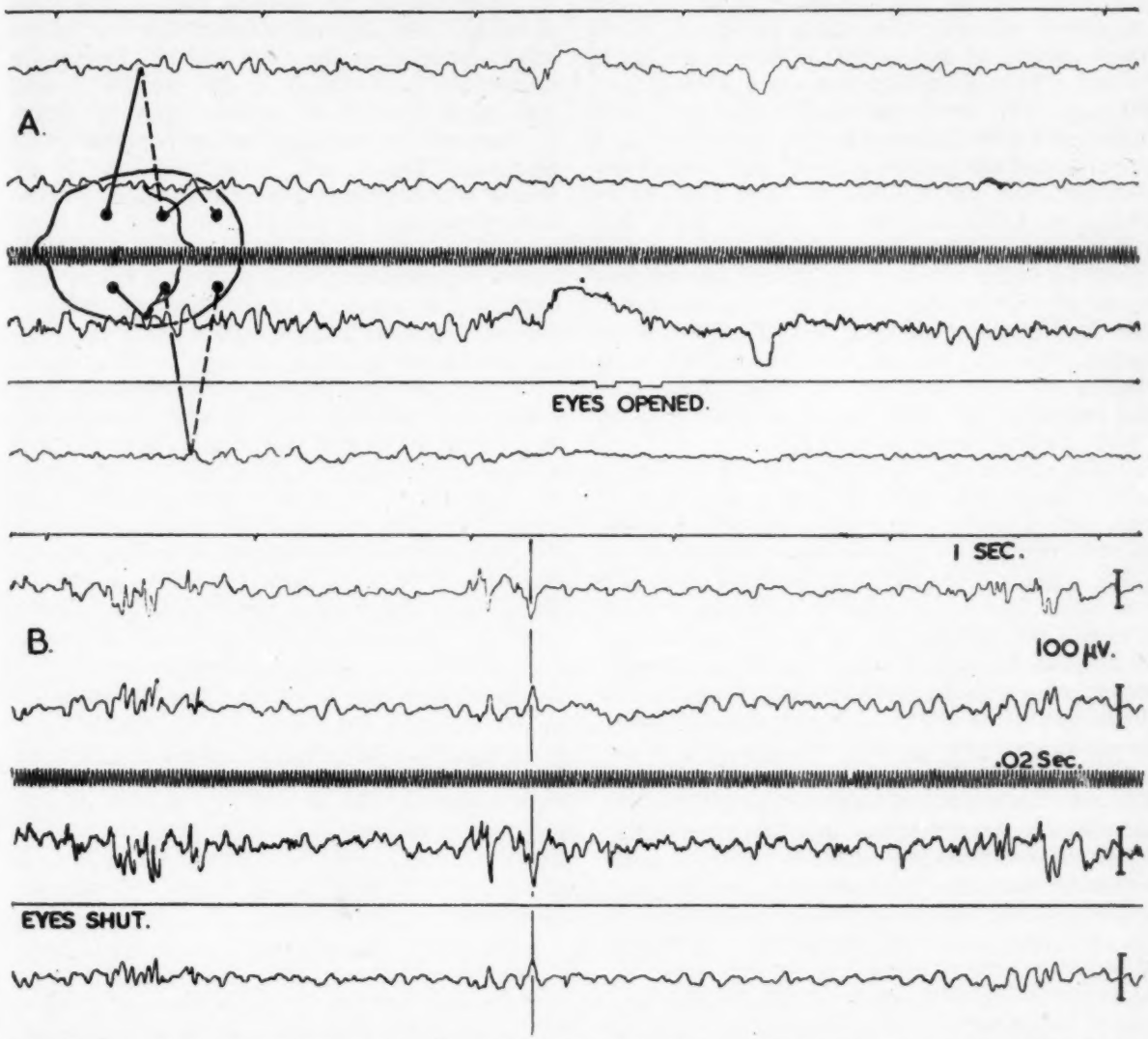

FIG. 1.—Shows in A a section from the resting EEG of the patient between seizures. There are some rhythms at 8 to 10 c/s. which are reduced on opening the eyes and there are some waves at 4 to 7 c/s. on both sides. The record in B shows groups of spikes which were accompanied by myoclonic jerkings. The vertical co-ordinate through the middle group of spikes shows that the activity was greatest under the middle electrode on both sides. In this and all following records the continuous and broken lines to the electrodes in the head diagrams indicate that if the electrode connected to the broken line becomes positive with respect to that connected to the continuous line an upward deflection will occur in the record.

time scales and calibrations are indicated on the records or below the figures.

Results

The EEG Between Seizures.—The EEG of this patient taken at the time of his second admission to hospital, after the myoclonic jerkings had begun, shows the same features as those reported by Dr. Hill in earlier records. There is a rhythm of 8 to 10 c/s. which is largest in the parieto-occipital regions and is reduced in size when the eyes are open, and there are some rhythms of low voltage with a frequency of 4 to 7 c/s. which appear on both sides without any clear location. There are no rhythms of less than 4 c/s. of significant size, and the record shows little change after overbreathing for three minutes. A section from the record before overbreathing is shown in Fig. 1A.

The EEG During Spontaneous Seizures.—In addition to the rhythms described above, the records show groups of spike-like discharges which occurred at intervals varying between a few seconds

and fifteen minutes and were accompanied by brief myoclonic seizures. The record in Fig. 1B shows three groups of these spikes. Each spike has a period of 30 to 50 milliseconds and an amplitude of 50 to 150 μV. In the records from this subject the spikes that occurred spontaneously always appeared larger on the left than on the right side, though the difference was not sufficient to suggest an abnormality or lesion confined to the left side. The direction of the deflections in Fig. 1B shows that when the spikes occurred the activity was greatest under the middle electrode on each side and that in the first phase of the spike discharge the central regions became positive with respect to other regions in front and behind. After these brief seizures there was no extinction of or interruption in the cortical rhythms.

Using surface plate electrodes, records were made of the muscle action potentials during the seizures; and such a record, from the quadriceps extensor muscles in the thighs, is shown, together with an EEG, in Fig. 2. The recording speed for this record was higher than for those in Fig. 1, and the waves in the EEG appear smoother and less like spikes than in the preceding records and they had a frequency during the seizure of thirty per second. The discharges in the EEG on the two sides appear to be synchronous and to have the same form within the limits of accuracy of this method of recording. The muscle action potentials also appear at the same time on the two sides, but they are considerably larger on the right side than on the left. This difference was observed constantly during spontaneous jerkings and agrees with the difference in the strengths of the jerkings that is observable clinically. The interval between the first of the spikes recorded in the EEG and the first of the muscle action potentials in this record is about 100 msecs. The length of this delay apparently depends on the events immediately preceding the discharge. This is seen towards the end of the seizure where there is a gap of 120 msecs. in the spike discharge in the EEG. After the 120 msec. interval there is a pair of spikes, and the muscle action potentials associated with them follow after only 50 or 60 msecs. The apparent delay will also depend upon the amplification used in recording the muscle action potentials, since, if the potential differences do not reach their maximum size immediately, and it is clear from the records that they do not do so, they will be detected earlier with a higher amplification. Using high amplifications no sign of any action potentials significantly different from the resting activity in the muscles was found in less than 80 msecs. if the seizure did not follow within a few seconds of a previous outburst. The interval between the stimulus and the onset of the myoclonic jerking in the leg was not altered by more than 10 msecs. if the tendon tap was applied to the arm instead of to the leg itself. In the record shown in Fig. 2 the muscle action potentials are grouped with the same frequency as the waves in the EEG, but this is an exception, and in other records there is little sign of such a close relation in the rates of discharge. In none of the records from this subject during seizures do the muscle action potentials recruit in any regular manner, and their shape is very variable.

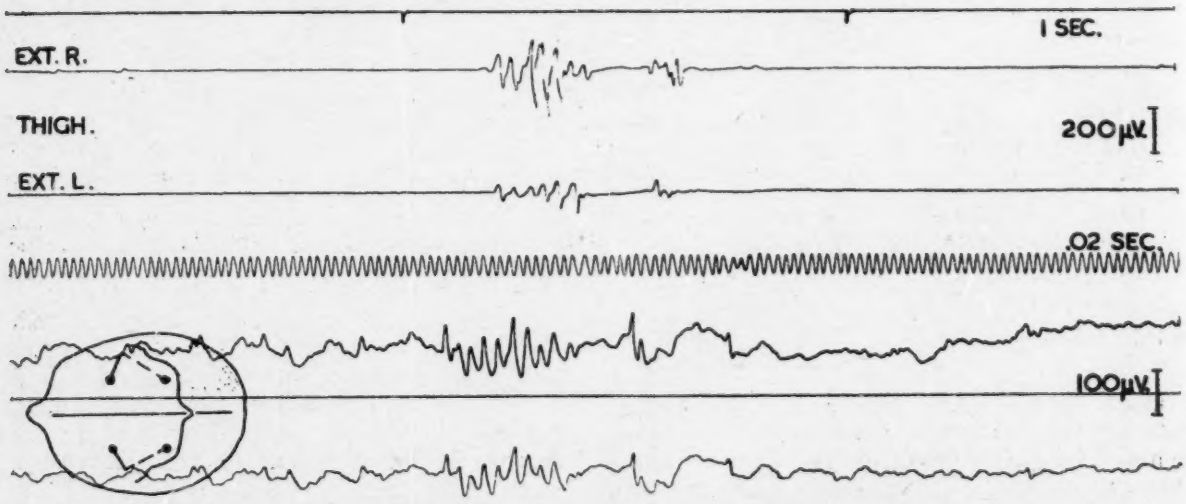

FIG. 2.—The two upper traces marked Ext. R and Ext. L record the muscle action potentials picked up from surface plate electrodes on the extensor aspects of the right and left thighs. The two lower traces show the spike discharge in the EEG during a spontaneous myoclonic jerking. The spike discharge in the EEG has a frequency of 30 per second and appears before the muscle action potentials.

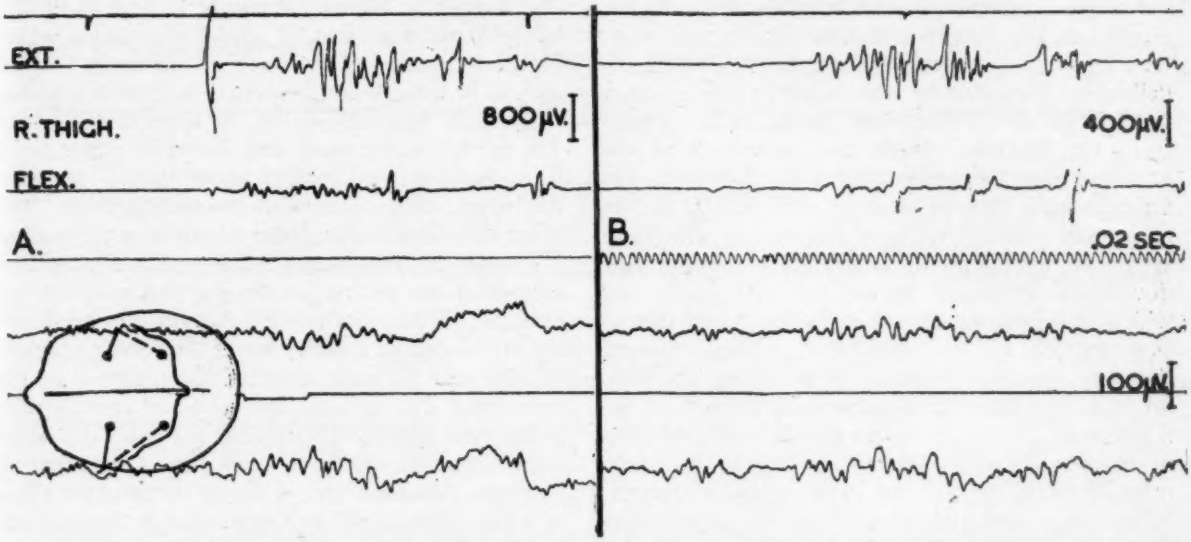

FIG. 3.—The records show the muscle action potentials from the extensor (Ext.) surface and flexor (Flex.) surface of the right thigh. In A the patellar tendon was tapped and, following the knee-jerk action potential in the extensor muscles, a myoclonic jerk occurs, beginning first in the flexor muscles. B shows a spontaneous myoclonic jerk beginning at the same time in the two muscle groups.

Records During Provoked Seizures.—When a sensory stimulus is applied to this subject a generalized myoclonic seizure usually results. A record of the EEG and the muscle action potentials during such a seizure, provoked by a tap on the right patellar tendon, is shown in Fig. 3A. The muscle action potentials were recorded from the extensor and flexor surfaces of the right thigh. They show the action potential during the knee jerk from the extensor muscles followed by those during the myoclonic jerkings from both flexor and extensor groups. This and similar records show that the myoclonic jerkings following the tendon reflex begin first in the flexor muscles of the knee. This order of discharge is not, however, characteristic of this type of myoclonic seizure when it occurs spontaneously. It may be seen from the record in Fig. 3B, made from the same muscle groups during a spontaneous myoclonic jerking, that the action potentials begin either synchronously in the two muscle groups or rather earlier in the extensors. The later onset in the extensors in the record in Fig. 3A is probably due to the period of inhibition that normally follows the tendon reflex. In these earlier experiments the location on the scalp of the area where the response to stimulation was greatest had not been worked out and the small size of the waves in the EEG in the records in Fig. 3 was probably due to the electrodes not being directly over this area of maximum activity.

The general level of relaxation of the subject was found to affect the strength and duration of the myoclonic jerkings greatly. When the subject was lying relaxed a tap applied to the patellar tendon produced a jerking that usually lasted little over a second. A similar stimulus applied one to two seconds after the subject had been told to clench both hands tightly resulted in jerking which was more violent than that in the relaxed state and which lasted for over five seconds. This facilitation of the jerkings when a voluntary effort coincided with a stimulus has been seen regularly, and no spontaneous variations of the same order of size occurred over short periods of time. The clinical examination of the tendon reflexes in this subject is difficult on account of the myoclonic jerkings that follow the reflex responses. In the record shown in Fig. 4A a tap was applied to the right patellar tendon and a large knee jerk action potential is followed by a spike discharge in the EEG and a myoclonic jerk. In Fig. 4B a stimulus applied to the left side produced a hardly detectable knee jerk action potential, but the subsequent myoclonic jerk was of the same size and has substantially the same form and duration as that which occurred when the stimulus was applied to the right side. This gave the appearance to clinical observation that the reflexes were brisker on the left than on the right side, the opposite to what was in fact the case.

In the records in Fig. 4, and in succeeding records where the stimulus was a tap with a tendon hammer, the black dots above the traces indicate the artefacts which show the time when the tendon hammer hit

the skin. The spike discharge in the EEG in the records in Fig. 4 shows features which have been seen repeatedly in these discharges. Following the deflection produced by the hammer contact is a pair of waves in which the deflection is upward from the baseline. With the connexions to the amplifier used this indicates that the back electrode on each side became positive with respect to the front one. Following these two waves, which are separated by about 30 msecs., there is a slower downward deflection lasting for 100 msecs. on which is superimposed the spike discharge that is accompanied by the myoclonic jerking. During the slow downward deflection the back electrode on each side became negative with respect to the front one. In certain circumstances the first pair of waves was not followed by either the slow negative wave or by the rapid spike discharge. When this occurred there was no generalized myoclonic jerking, but a second brief jerk, which was confined to the stimulated limb, occurred after the main reflex response.

The form of the initial pair of waves and the succeeding events in the response to stimulation is more clearly shown in the records in Fig. 5, made with a cathode ray oscillograph. Records A and B in this figure show the complete series of events, the tap on the tendon indicated by the dot above the trace, the initial double positive wave, the slower negative wave, and the rapid "spike" discharge with a frequency of thirty per second. In both records the spike discharge slows down considerably just before it ceases. Records C and D in this figure show examples of initial discharges which occurred alone, and the form of the waves may be seen to be closely similar to that in records A and B, where they were followed by the other disturbances. The initial double wave was found to occur alone if a stimulus was applied soon after a previous discharge, either provoked or spontaneous. The effect of repeated stimulation about once per second is shown by the record in Fig. 6. The second section of the record follows the first without any interval. When first applied the stimulus produced the initial double positive wave, the slower negative change, and the train of waves accompanied by the myoclonic jerking. As the series of stimuli continued, the negative change and the spike discharge became smaller and the jerkings almost disappeared. It seems, therefore, that in the response in the EEG to a tap on a tendon two parts may be recognized. The first part consists of the double wave whose size and form do not seem to be greatly affected by rates of stimulation up to once per second. The second part consists of the slower wave and the spike discharge, both of which tend to disappear after several stimuli have been applied at one second intervals. To see if further differentiation between these parts of the discharge could be made, the effect was tried of compressing the carotid artery on one side. The pressure was maintained for up to seventy-five seconds, and during this time the patellar tendon on the opposite side of the body was tapped at intervals. When this was done no

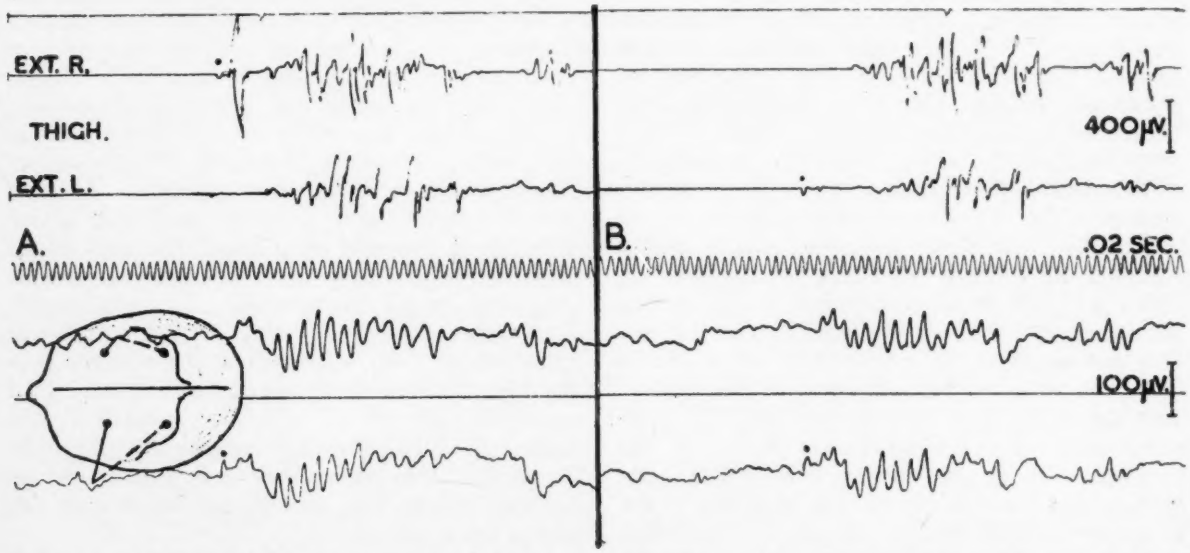

FIG. 4.—The records show the results of taps applied to A, the right, and B, the left, patellar tendon. Though the knee-jerk action potential following the tap on the left side is hardly perceptible, the following myoclonic jerk is as large as that which followed a much stronger knee jerk on the right side. (The black dot above the records indicates the artefact produced electrically by the contact of the tendon hammer with the skin.)

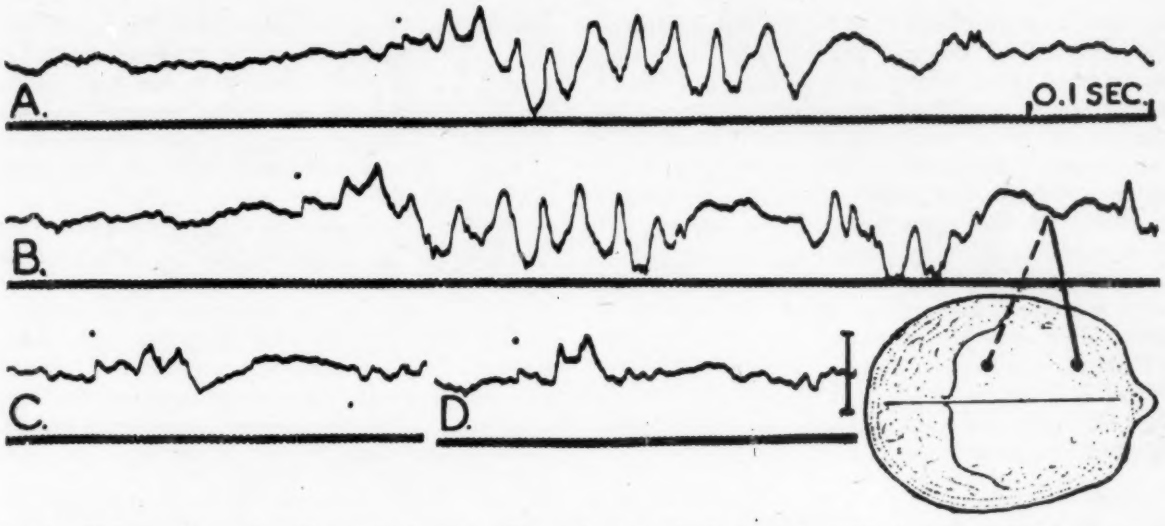

FIG. 5.—The records, made with a cathode ray oscillograph, show the form of the EEG discharge following a tap on a tendon. The black dots indicate the contact of the hammer with the skin. This is followed by a pair of waves during which the back electrode on the head became positive with respect to the front one. In A and B the back electrode then became negative and a train of spikes followed which was accompanied by a myoclonic jerk. In C and D no negative deflection occurred, and no train of spikes or myoclonic jerking followed. The calibration mark in D shows 100 μV.

difference was found in the ease with which jerkings or discharges in the EEG could be provoked and no alterations were found in the spontaneous cerebral discharges. This last observation suggests that although the subject stated that he had some sensation of light-headedness during the first period of compression, the degree of cerebral anæmia produced was not great and that therefore the value of the results is limited.

Attempts were made to measure the delay between the stimulus and the first most constant part of the response in the EEG more accurately than was possible in records such as those in Fig. 5. For this purpose the contact of the hammer with the skin of the subject was arranged to start the time sweep on the cathode ray tube and the sweep was photographed on stationary bromide paper. Using this method it was found that the interval between tapping a patellar tendon and the first of the waves in the EEG varied between 30 and 35 msecs. Since part of this variation was probably due to the uncertainty of the delay between the time the hammer touched the skin and the stretching of the muscle, some method was sought of timing the actual stimulation more accurately. An electrical stimulus to a peripheral nerve, strong enough to be maximal for the motor fibres in the nerve, was found to produce closely similar discharges in the EEG and the same type of myoclonic jerkings. The only difference was that when stimulating the ulnar nerve at the wrist the delay between the stimulus and the myoclonic jerk in the arm was as long as 250 to 300 msecs., about 150 to 200 msecs. longer than that between a tap on the patellar tendon and the myoclonic jerk in the thigh muscles, or between a tap on the tendon of the biceps muscle in the arm and the following jerk in the anterior tibial muscles. Since no data are available on the delay between a tendon tap applied to the arm and the following myoclonic jerk in the arm itself, it is not possible to say how far this difference is due to the difference in the site of stimulation and how far it is due to the type of stimulus applied. Using electrical stimulation the characters of the first part of the response in the EEG were so constant that in later experiments attention was concentrated almost entirely on this initial part of the discharge. So far it has been assumed that the discharges in the EEG following sensory stimulation are of cerebral origin. Other sources of potential difference on the scalp likely to be encountered in experiments such as these are twitches of scalp muscle and, when an electrical stimulus is used, spread of current from the point of stimulation. Though these sources of artefact have not been excluded directly, the characters of the responses to be described suggest strongly that the responses are cerebral in origin and are not due to either of the other causes mentioned.

Distribution of Potentials.—With any one of the electrode positions used in these experiments no

significant variation was found in the distribution of the potential differences on the scalp following stimulation, either during the periods up to two and a half hours covered by individual experiments or the period of a year covered by the series of experiments. Since the distribution of the response did not alter, it was possible to plot the potential gradients on the scalp by recording successively from a number of electrodes with only two recording systems. When the results obtained in this way were compared with those from experiments in which four recorders were used simultaneously no difference was found.

In Fig. 7A, B, and C are shown records taken from four electrodes placed along the midline of the head, one over the vertex, one 6 cm. behind this, and two others 6 and 12 cm. in front of it. The record in A shows the response to a single stimulus applied to the left lateral popliteal nerve at the head of the fibula. The point at which the response begins is difficult to define on account of the irregularity of the baseline due to spontaneous activity from brain and scalp muscle.

The records in B and C show superimposed the responses to fifty successive shocks, each maximal for motor fibres, applied at a rate of one per second to the same nerve at the same point as in record A. Record C was made after record B, not simultaneously. The time scale for records B and C, which is shown below record B, was slightly slower than that used for A. The time between the stimuli and the responses does not vary by more than two milli-

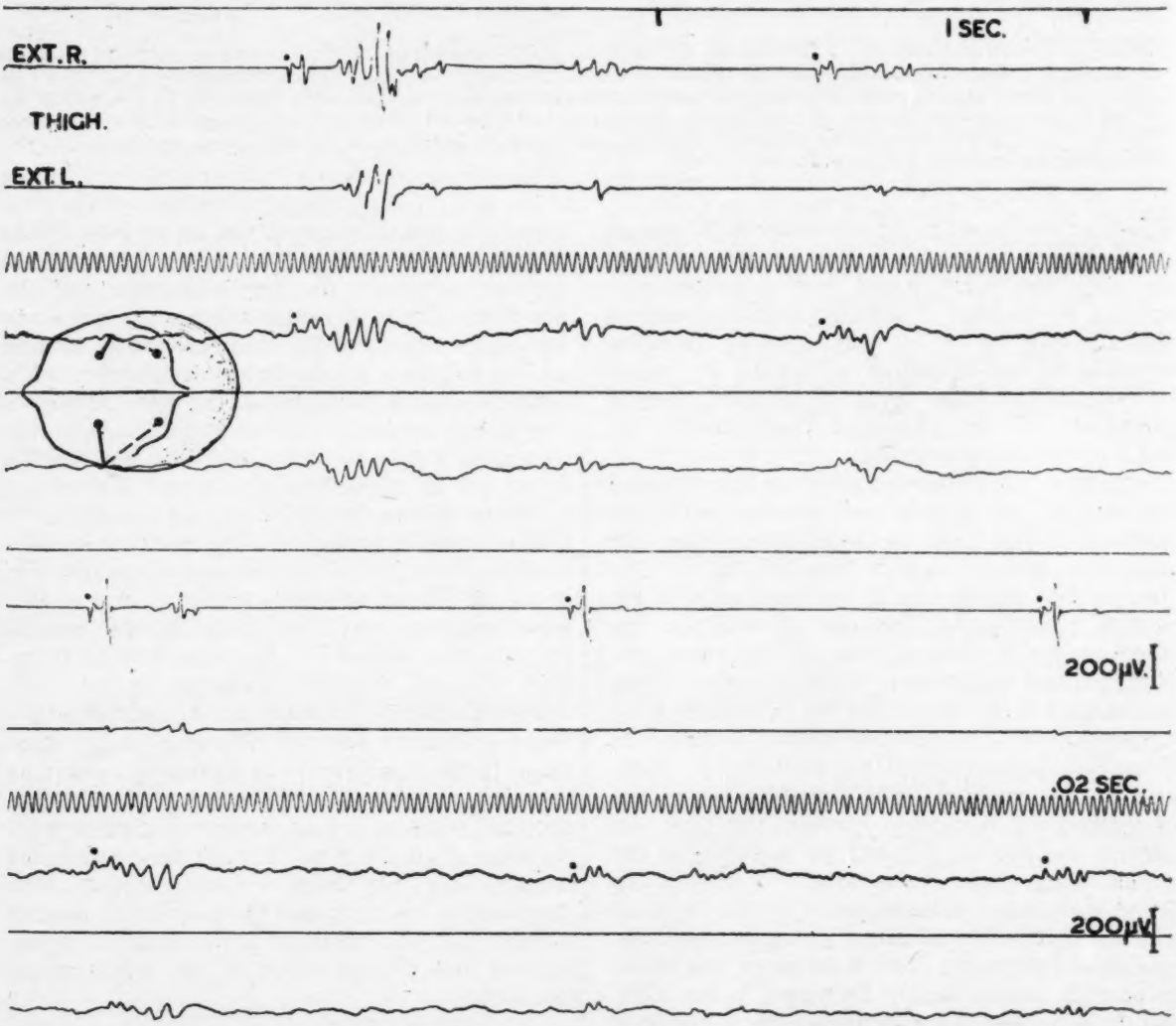

FIG. 6.—The records show the effects of a series of stimuli applied at intervals of one second to the right patellar tendon. The initial pair of waves in the EEG, about 30 msecs. after the stimulus artefact, occurs in every case, but the spike discharge and the myoclonic jerking become smaller and almost disappear.

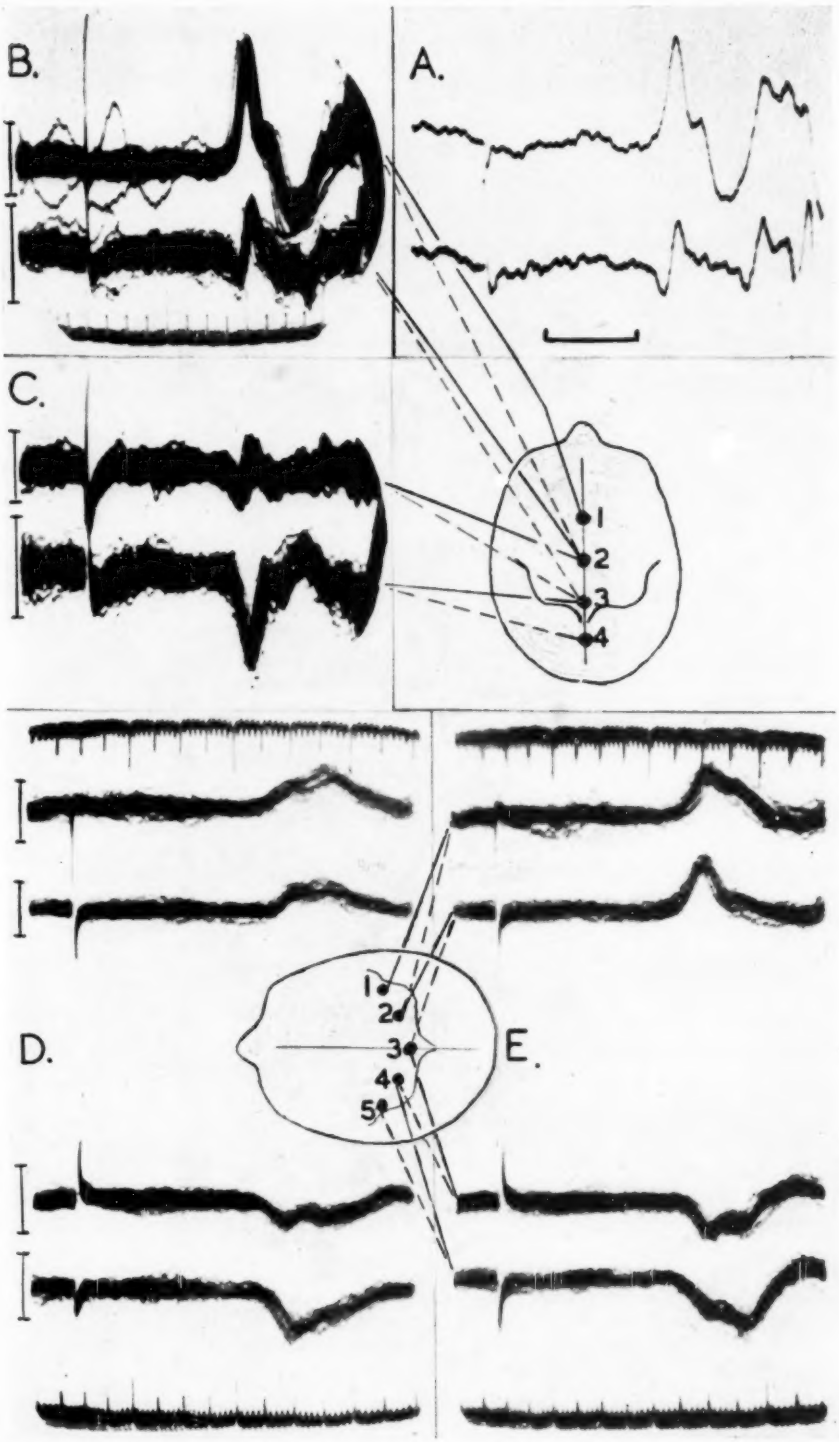

FIG. 7.—The records show the responses recorded from scalp following electrical stimulation of the lateral popliteal nerve at the head of the fibula. In A is shown the response to a single stimulus; in B, C, D, and E are shown superimposed the responses to 50 stimuli at one second intervals. Records B and C, made successively, show a maximum of activity, with the active area initially positive, between electrodes 2 and 3. Records D and E show a maximum of activity near electrode 3, on the midline. In D the stimulus was applied to the right side and the activity reaches a peak first in the records from the left side of the head. In E, where the stimulus was applied to the left side, the peak occurs first on the right side. The latency from the stimulus to the start of the response is between 33 and 36 msecs. The time mark below A shows 20 msecs. and the time scales in B to E show intervals of 1, 5, and 20 msecs. The calibration marks at the left hand ends of the records show the deflection due to 20μV. in A, B, and C, and 40 μV in D and E. In A, B, and C the electrodes were 6 cm. apart, and in D and E 4 cm. apart. In both cases electrode 3 was on the vertex.

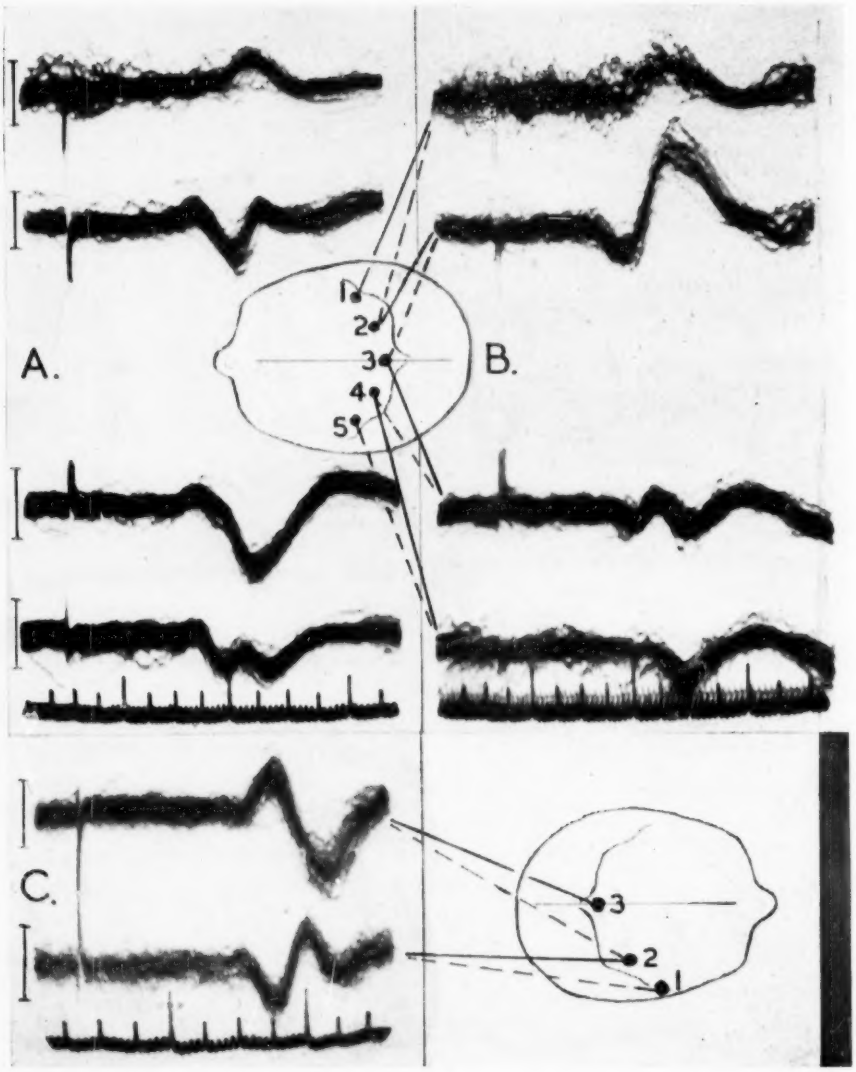

FIG. 8.—The records show the responses to stimulation of the right, A, and the left, B, ulnar nerves at the wrists. The deflections appear largest in the leads from the side of the head opposite to the stimulus. In C the electrodes were on the vertex and 8 and 16 cm. from it on a line parallel with the surface marking of the central sulcus. The activity following a stimulus to the left ulnar nerve at the wrist has a peak 8 cm. from the vertex, nearer to electrode 2 than to either of the others. The time scales show intervals of 1, 5, and 20 msecs. The calibration marks for A and B indicate 40 μ V, and for C 30 μ V.

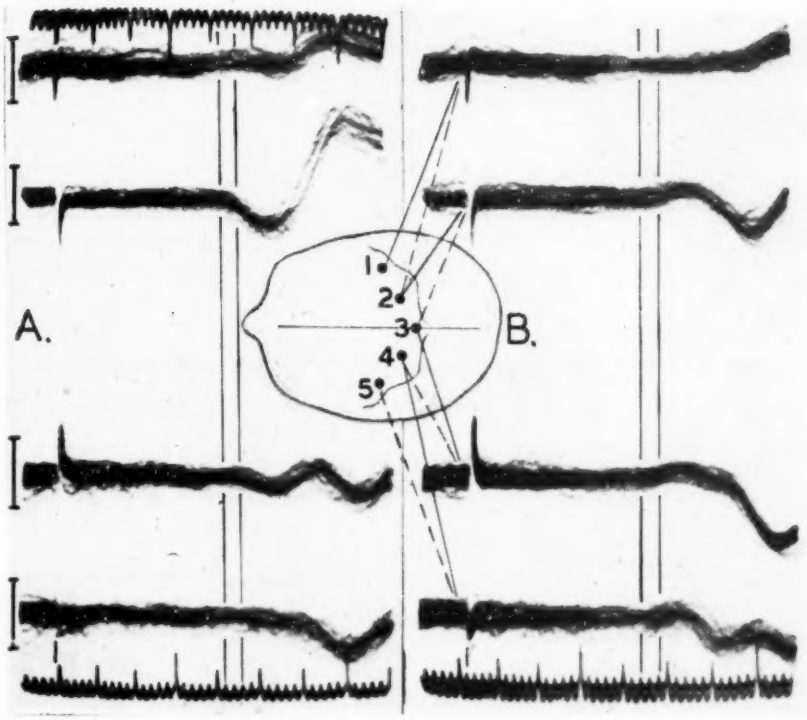

FIG. 9.—The records show the responses to stimuli to the left ulnar nerve at the wrist, A, and to the right ulnar nerve at the wrist, B, on a faster time scale than in Fig. 8 A and B. The latency from the stimulus to the beginning of the response is 21 to 23 msecs., and the first activity that appears on the same side of the head as the stimulus, and which is not electrical spread from the opposite side, begins 7 to 8 msecs. later. The time scales show intervals of 1, 5, and 20 msecs., and the calibration marks 40 μ V.

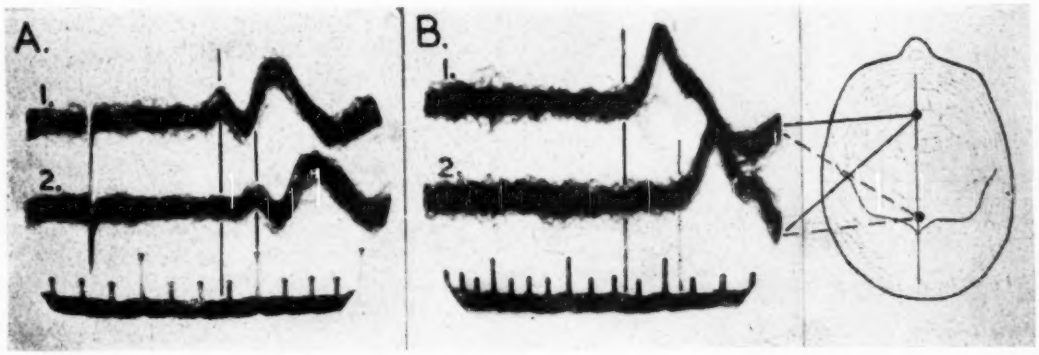

FIG. 10.—The records show in A the difference of 6 msecs. in the latency of the response following stimulation of the ulnar nerve at the elbow, trace 1, and at the wrist, trace 2. In B is shown the difference of 10 to 11 msecs. in the latency of the response following stimulation of the lateral popliteal nerve in the popliteal fossa, trace 1, and the posterior tibial nerve at the ankle, trace 2. The time scales show 5 and 20 msecs. intervals.

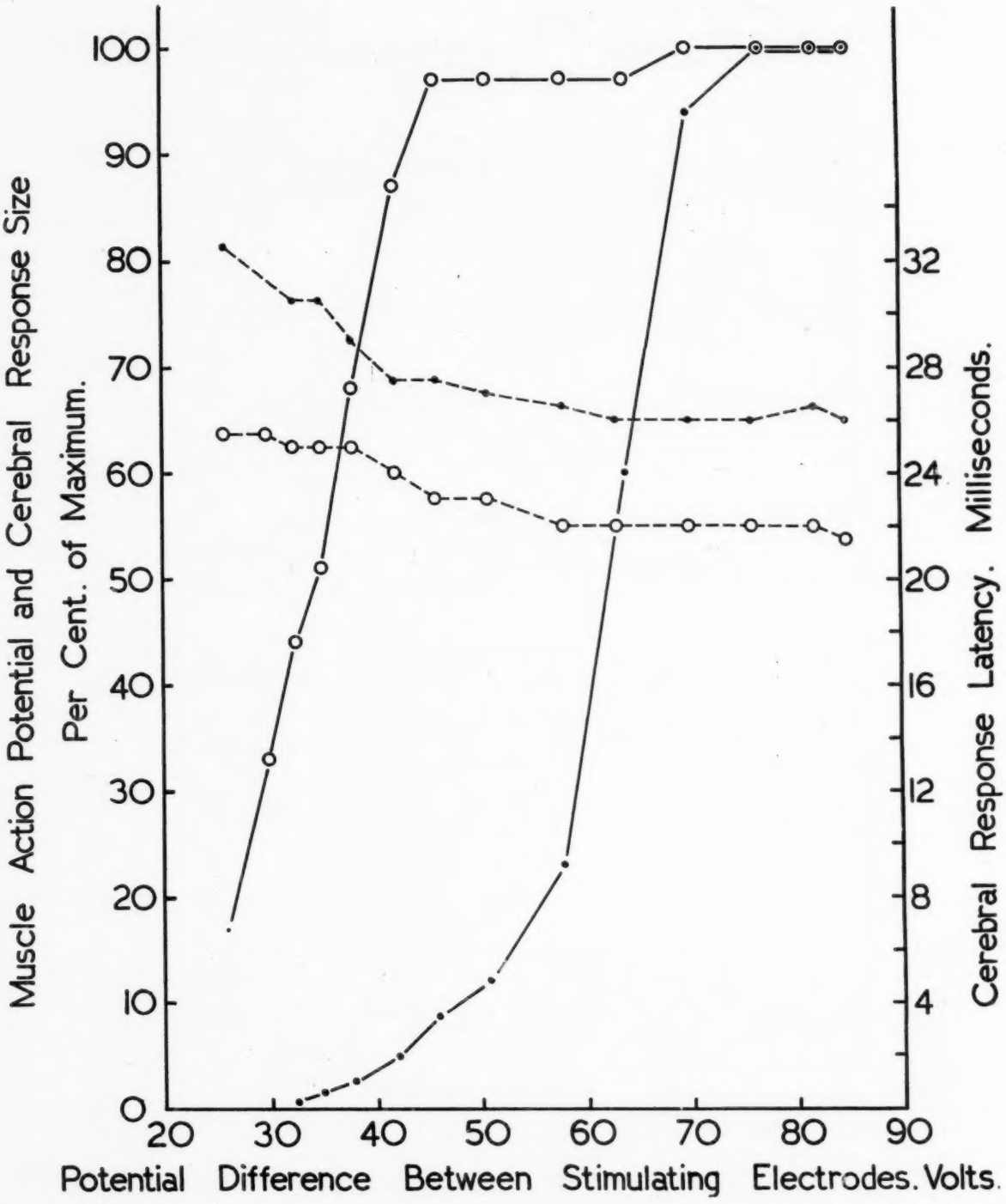

FIG. 11.—The graph shows the relation of the potential difference between the stimulating electrodes, with the cathode applied to the ulnar nerve at the wrist, and (1) the size from baseline to peak of the cerebral response (open circles and continuous line), (2) the size from baseline to peak of the action potentials from surface electrodes over the M. abductor minimi digiti in the hand (dots and continuous line), (3) the latency from the stimulus to the start of the cerebral response (circles and broken line), and (4) the latency from the stimulus to the first positive peak of the cerebral response (dots and broken line). Each point is the mode of the results of fifty stimulations and probably closely approaches the mean value.

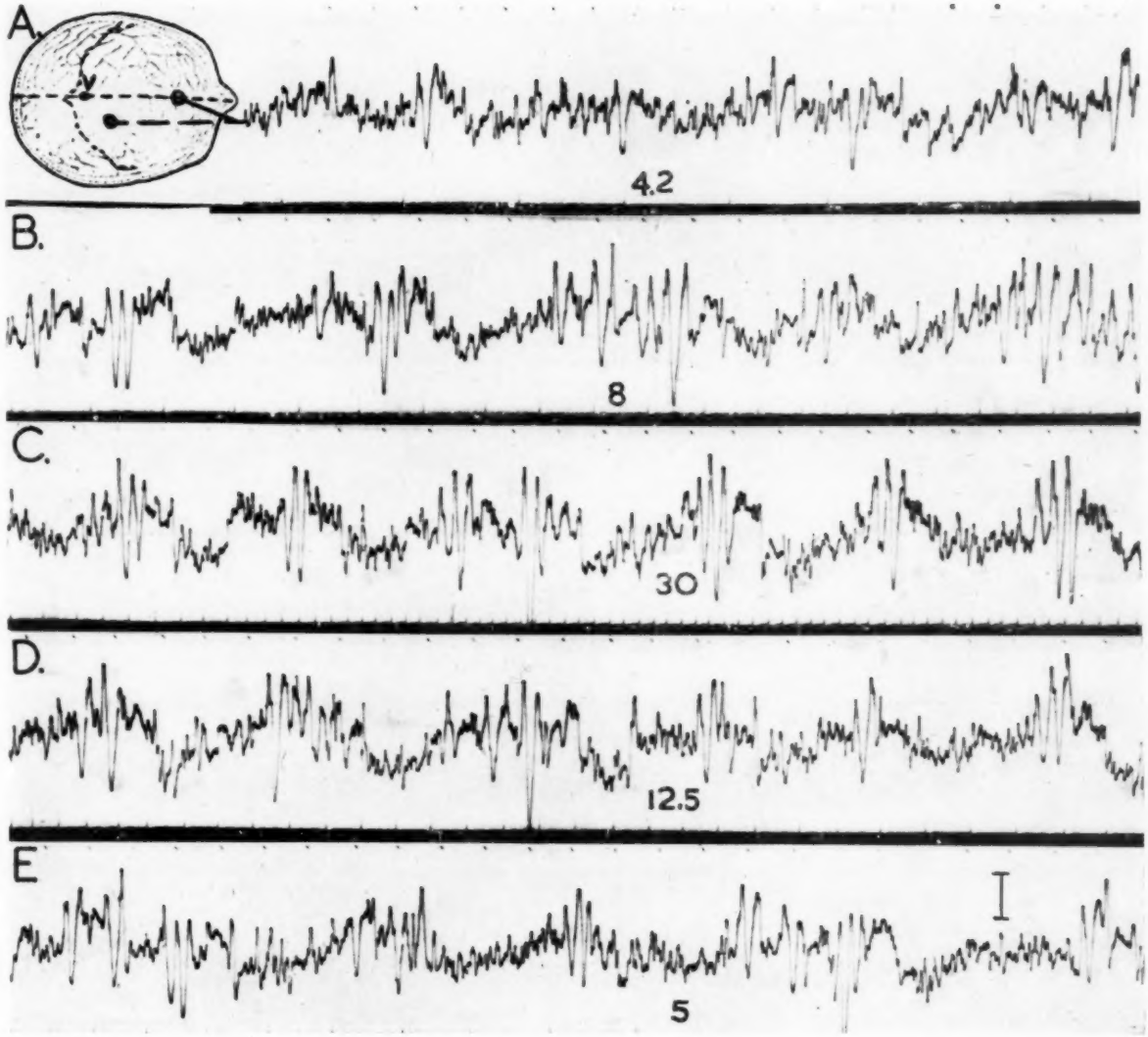

FIG. 12.—The record shows the EEG during stimulation of the left ulnar nerve at frequencies from 4 to 30 per second. The rate of stimulation is shown at the centre of each record and the spikes at the bottom of the records show the position of the stimuli. At a rate of 30 per second the stimuli provoke large bursts of oscillations at intervals of 0·3 to 0·4 of a second and with a frequency of 30 per second. These outbursts were accompanied by particularly violent myoclonic jerkings. The marks at the top of the records indicate intervals of 0·1 seconds and the calibration mark in E represents the deflection due to 50 μ V.

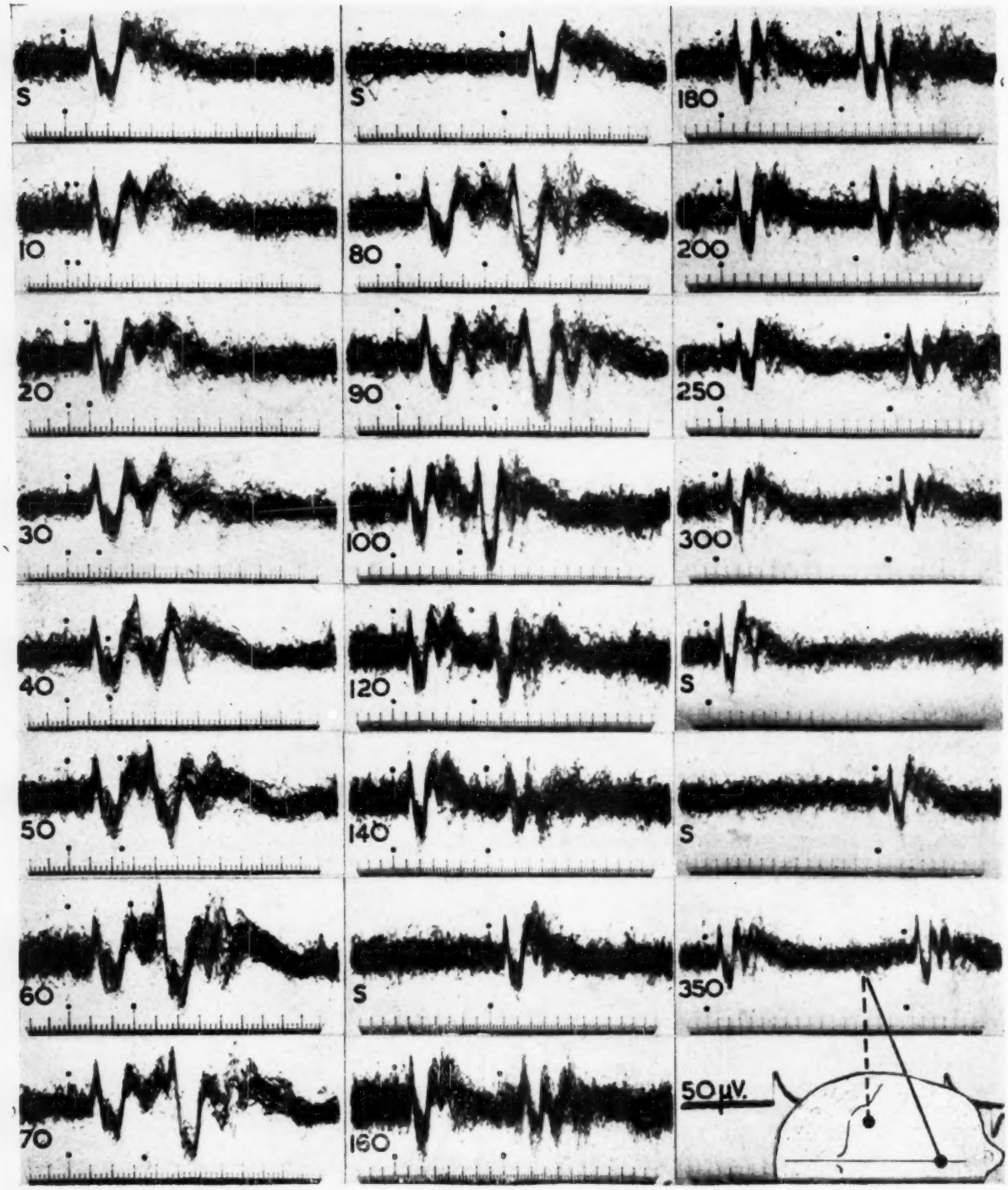

FIG. 13.—The records show the responses to a pair of shocks separated by intervals of from 10 to 350 msecs. S indicates single control stimuli, and in each record fifty single shocks, or pairs of shocks at the separation marked on the record, were applied at one second intervals. The black dots indicate the stimulus markers in the time scale and the stimulus artefacts in the cerebral response. The response to the second shock of the pair is depressed at a separation of the shocks of 10 to 30 msecs., it is facilitated from 60 to 100 msecs., depressed and delayed at 140 msecs., and almost returned to normal at 300 to 350 msecs. The time scales indicated 5 and 20 msec. intervals.

seconds in either direction in these records, and the form of the earlier phases of the response shows little variation. The sense of the deflections in the records in B and C shows that during the response the activity was maximal between electrode 3, at the vertex, and electrode 2, six centimetres in front of it. During the first phase of the response this area of maximum activity becomes positive with respect to other parts in front of and behind it.

The records shown in Fig. 7D and E were made with the electrodes arranged on lines parallel with and 3 cm. in front of the surface markings of the central sulci. One electrode was placed on the midline and the others 4 and 8 cm. from it on each side of the head. The records were made simultaneously from both sides of the head during stimulation of one or other lateral popliteal nerve at the head of the fibula. The stimulus was applied first to the right side, Fig. 7D, and then to the left, Fig. 7E, and in both cases electrode 3, on the midline, became positive with respect to the others. The response also shows an asymmetry which is related to the side of the body to which the stimulus was applied. The first phase of the response consists of a positive wave that lasts for 15 to 20 msecs. on which are superimposed two briefer waves separated by 5 to 7 msecs. In the record in Fig. 7D, where the stimulus was applied to the right lateral popliteal nerve, the first of the two briefer waves is larger than the second one in the records from the left side of the head. In the records from the right side of the head the first of the brief waves is smaller than the second one. The difference is clearest in a comparison of the record from electrodes 4 and 5 and that from electrodes 1 and 2. In Fig. 7E, when the left lateral popliteal nerve was stimulated, the opposite is the case, and in the records from the right side of the head the first of the two rapid waves is larger than the second. Thus the response to a stimulus applied to a leg appears as a potential change that is maximal about 3 cm. in front of the vertex and near to the midline. Also it seems that the response reaches its peak sooner on the side opposite to that stimulated than on the same side as the stimulus.

The records in Fig. 8A and B, made with the same electrode positions as for those in Fig. 7D and E, show the responses to stimulation of the right and left ulnar nerves at the wrists. The form of the response is different from that which follows stimulation of the lateral popliteal nerve, and the response is much larger on the side of the head opposite to the arm stimulated than on the same side. When the stimulus was applied to the right ulnar nerve, Fig. 8A, the greatest deflection appears in the lead from electrode 3, on the midline, and electrode 4, four centimetres lateral to it on the left side. The form of the deflections in the lead from electrodes 4 and 5, on the left side, 4 and 8 cm. from the midline, suggests that the disturbance was occurring between these electrodes at first nearer to electrode 5, when the deflections at the beginning of the response are in the same sense, and later moving medially to a point nearer to electrode 4, four centimetres from the midline, when the deflections are in opposite sense. When the left ulnar nerve was stimulated, Fig. 8B, the greatest deflection appears in the record from electrodes 2 and 3, on the right side of the head. In all these records electrodes 1 and 5, which were 8 cm. from the midline, were too close to it to allow the lateral extent of the area of maximal activity to be defined and all that may be said is that it was probably centred nearer to electrode 1 than to electrode 2, or nearer to electrode 5 than to electrode 4.

In Fig. 8C is shown a record taken from the right side of the head with electrodes over the same line parallel to the surface marking of the central sulcus but 8 and 16 cm. from the midline. Here a stimulus to the left ulnar nerve at the wrist produces a deflection starting in opposite sense in the two traces, suggesting that the activity was at first maximal near to electrode 2, common to the two recording channels, and showing that the scalp in this area became positive with respect to other parts. In the later phase in which the active area has become relatively negative it has moved laterally so that it lies between electrode 2, and electrode 1, eight and sixteen centimetres from the midline respectively. The same distribution with a maximum about 8 cm. from the midline has been found when stimulating the right ulnar nerve and recording from the left side of the head. Experiments with an antero-posterior arrangement of the electrodes showed that the area of greatest activity was in this instance, as when the leg was stimulated, centred about three cm. in front of the surface marking of the central sulcus. This distribution of the responses to stimulation of the arm and leg suggests that they are of cerebral origin. There is no clear reason why the response, if it was a reflex twitch of scalp muscle, should appear near the vertex, where there is least muscle, after a stimulus to the leg, or why, when stimulating the arm, it should appear largest on the opposite side of the head 8 cm. lateral to the midline.

The question arises as to what part of the potential differences picked up from electrodes on the same side of the head as the limb stimulated is due to cerebral activity on that side, and what part is due to spread of current from the much greater activity on the side of the head opposite to the limb stimulated. With the electrode arrangement shown in

Fig. 9 cerebral activity of the same polarity in homologous areas on the two sides of the head, for example under electrodes 1 and 5, would be recorded in the records from the two sides as deflections in opposite sense. If there were only one maximum of activity, for example under electrode 5 in Fig. 9, any current flow affecting the electrodes on the opposite side of the head would produce deflections in the same sense on the two sides. Using these criteria it may be suggested from the records in Fig. 9 that both effects are occurring. These records were made with the same electrode positions and the same stimuli as were used for the records shown in Fig. 8A and B, but were made on a faster time scale.

In part A of Fig. 9 is shown the response to a stimulus applied to the left ulnar nerve. The deflection begins in the trace from electrodes 2 and 3 about two milliseconds before there is any deflection in the leads from the left side. The first deflection appearing from the left side is in the lead from electrodes 3 and 4 ; it is in the same sense as that from the right side and is therefore probably electrical spread of the activity from the right side. Deflections then appear in both traces from the left side of the head and they are in opposite sense to those from the right side of the head. These deflections might be due to either fresh cerebral activity starting on the left side in addition to that already present on the right side, or to a single peak of activity near to electrode 3, on the midline.

The records in Fig. 8 suggested that the initial disturbance following stimulation of the left arm was centred between electrodes 1 and 2. If the disturbance in the records in Fig. 9A originated in the same place and then moved to near electrode 3, a point should occur in the record where the traces from electrodes 1 and 2 and from electrodes 2 and 3 would move in opposite sense with equal amplitudes. Since this does not occur it may be suggested that the activity in the initial part of the response remains centred lateral to electrode 2 and does not move to electrode 3, on the midline. If the centre of activity, initially on the right side, does not move up to the midline, it seems that the deflection which appears in the record in Fig. 9 from electrodes 4 and 5, on the left side of the head, the same side as that of the limb stimulated, indicates fresh cerebral activity on the left side of the head. This fresh activity on the left side starts about 7 to 8 msecs. after the activity first appears on the right side of the head, and in the initial deflection of the left sided activity electrode 5 became negative with respect to electrode 4.

In Fig. 9B when the right ulnar nerve was stimulated a similar series of events occurred but with the activity appearing last under electrode 1. This suggests that here also there was cerebral activity on the same side of the head as the stimulus, appearing later than the activity on the side of the head opposite to the stimulated limb. In these records in Fig. 9 there is evidence of a limited spread of the active area in a medial direction. In the record in Fig. 8C there is evidence of a similarly restricted spread in a lateral direction, and in the records in Fig. 7B and C of a movement of the area of maximum activity in a backward direction from nearer electrode 2 to nearer electrode 3.

Further experiments with the electrodes separated by three centimetres along the midline of the head showed no evidence of movement of the active area over distances greater than three centimetres in an antero-posterior direction. It seems, then, that three forms of spread may be detected in these records. First there is the local spread for up to three centimetres or less around each area of maximum activity. Secondly there is the purely electrical conduction of currents from an area of relatively great activity to surrounding less active or inactive areas. Thirdly there is the appearance of activity on the same side of the head as the stimulus, up to 8 msecs. later than the primary activity on the side opposite to the limb stimulated and of opposite sign to this.

Afferent Pathways.—When a nerve was stimulated at the periphery the delay between the stimulus and the response in the EEG was found to be longer than when the same nerve was stimulated proximally. This difference in the delays has been taken as evidence that the response on the scalp is produced by a disturbance propagated in nerve and not by spread of the stimulating current, and it has been used to make an estimate of the conduction velocity in the nerve between the two points of stimulation. Measurements of the total delay have been made from the stimulus escape in the record to the start of the response and to the peak of the first positive wave. The measurements were made to the middle, or the darkest part, of the thick line produced by the superimposed records ; they are therefore the mode of fifty responses and, although no experiments have been carried out to determine the distribution of the sweeps in the thick record, it seems likely that this is close to the mean position of the trace. Though the delay from the stimulus to the response varied little in any one experiment, it varied from one experiment to the next. That part of this variation may have been due to differences in the positions of the electrodes on the head is suggested by the difference between the delay from the stimulus to the start of the response in the record

in Fig. 8C, and that in trace 2 in Fig. 10A. In both cases the stimulus was applied to the ulnar nerve at the wrist, but in Fig. 8C, where one of the recording electrodes was near to the active area, the delay was 23 ± 1 msecs., whereas in Fig. 10A, where the recording electrodes were farther from the active area, the delay was 25 ± 1 msecs. The range of latency from the stimulus to the start of the response that was found for the different sites of stimulation was from 19 ± 1 msecs. at the elbow to 24 ± 1 msecs. at the wrist, 35 ± 2 msecs. at the head of the fibula, 32 ± 2 msecs. in the popliteal fossa, and 43 ± 2 msecs. at the ankle.

For measurements of conduction velocity the nerve was stimulated at two points and the response recorded from a fixed pair of electrodes on the head. Fig. 10A shows records made in this way with stimuli applied to the ulnar nerve at the elbow, trace 1, and at the wrist, trace 2. The difference in the delay to the start of the responses is 5 msecs. and that to the first peak, shown by the vertical lines on the record, is 6 msecs. The distance between the stimulating points was 28 cm. giving conduction velocities of 56 and 47 metres per second respectively. Fig. 10B shows the result of a similar experiment where the stimuli were applied to the medial popliteal nerve in the popliteal fossa, trace 1, and to the posterior tibial nerve at the ankle, trace 2. Here the difference in the delay from the stimulus to the first part of the rise in each response is about 11 msecs. The difference in the delays from the stimuli to the peaks of the responses is less, about 10 msecs. The distance between the two stimulating points was 46·5 cm., giving conduction velocities of 42 to 43 metres per second and 46 to 47 metres per second according to the point on the response used for the measurement.

There are several probable sources of error in such estimates of conduction velocity. The measurement of the distance between the two stimulating points over the surface of the limb probably does not give the length of nerve between the two points to within better than one centimetre in thirty, though no figures relating to such a measurement in the limbs have been found. The exact point of stimulation is uncertain owing to the spread of the stimulating current in the tissues, and experiments were made to see what was the order of this spread. If stimulation is occurring at a point on the nerve away from the electrode there must be some point at which the spreading current is just strong enough to excite the nerve. Any weakening of the stimulus would be expected to bring this point nearer to the electrode, and to increase the actual distance over which the resulting impulses would have to be conducted and therefore also the delay between the stimulus and the response. In the graph in Fig. 11 the delay between the stimulus and the first part of the rise of the response has been plotted as a function of shock strength. There was a slight but probably not significant increase in the delay between the shock and the cerebral response as the shock strength was reduced from 84 to 82 volts. A further reduction from 82 to 65 volts caused no increase in the delay. Since a twenty per cent. decrease in the size of the shock did not produce an increase in the delay it seems likely that, with the shock strengths used in these experiments, spread of the stimulating current was not a major source of error. The measurements of differences in time may be made to better than plus or minus 1 msec. Although this is a small part of the total delay from stimulus to cerebral response, it is large in comparison with the differences of 5 to 6 msecs. in the delays from stimuli at the wrist and elbow, and probably it accounts for a great part of the errors.

A further source of error lies in the fact that when the nerve is stimulated peripherally fewer fibres will be excited than when it is stimulated proximally after any branches have joined it. If the excitation of fewer fibres in the nerve causes a slower rate of rise in the cerebral response this would apparently increase the delay following the peripheral stimulus, and make greater the interval between the response due to it and that due to the proximal stimulus. To examine this source of error, and to try to estimate the threshold to electrical stimulation of the afferent fibres concerned in the response, the ulnar nerve was stimulated at the wrist and the cerebral response was recorded from over the appropriate area of scalp. At the same time a record was made of the action potential in the M. abductor minimi digiti in the hand and of the potential difference between the stimulating electrodes. Fifty records were superimposed, and in Fig. 11 there are shown plotted as a function of the potential difference between the stimulating electrodes, the delay from the stimulus to the start and to the peak of the cerebral response, the size of the cerebral response from baseline to peak, and the size of the muscle action potential from baseline to peak. The sizes are plotted as a percentage of the maximal sizes of the responses, and the value for each point on the graphs is the mode of fifty records. When the stimulus fell below 60 volts the delay from the stimulus both to the start and to the peak of the cerebral response began to increase and a significant change of 1 msec. occurred before the size of the cerebral response had fallen significantly. Thus, although there is no reduction in the size of the response to the more

peripheral stimulus in the records in Fig. 10A and B, there may still be a greater central delay than after the proximal stimulus, if the effects of stimulating a nerve trunk where it is smaller are similar to those of reducing the shock strength and stimulating fewer fibres in the nerve. The values of conduction velocity measured were between 42 and 56 metres per second, and the overall accuracy was probably about plus or minus thirty per cent.

The last source of error discussed seems likely to be large and it would give rise to lower values of conduction velocity than the true one. Measurements of the conduction velocity in the motor fibres in the same stretch of nerve in this subject and in healthy subjects where there was no question of central delay giving a low result have given figures of 45 ± 10 metres per second. If in fact the velocities obtained for the afferent fibres are low, this seems to suggest that they might have a conduction velocity higher than that of the motor fibres in the same nerve and also a lower threshold.

In the graph in Fig. 11 it may be seen that when the strength of the stimulus to the ulnar nerve dropped below 75 volts the action potential from the M. abductor minimi digiti, recorded from surface electrodes, began to fall off in amplitude in the usual sigmoid manner and at a shock strength of 46 volts had fallen to less than one tenth of its maximum size. At this size of shock the cerebral response was not significantly reduced in size. This suggests two possibilities, first that the afferent fibres concerned have a lower threshold to electrical stimulation than the motor fibres in the same stretch of nerve, or secondly that so long as more than a certain number of fibres is stimulated there is an explosive cerebral response which tends to reach a maximum size. That the first is the more likely explanation is suggested by the fact that when the size of the cerebral response does begin to fall it does so progressively, in a similar manner to that of the motor response. If an explosive cerebral response were occurring it might be expected that the response would disappear suddenly when the number of fibres stimulated fell below a critical value. The points at which the muscle response and the cerebral response begin to fall correspond to 77 and 46 volts respectively. These figures give the relative thresholds for stimulation of the least sensitive fibres in each group and the values for the majority of the fibres in each group have a similar ratio. No information has been obtained about the most sensitive fibres as the cerebral response became smaller than the irregularities in the trace. At the last point, corresponding to a stimulus strength of 26 volts, it could be said that there was still a cerebral response present, although its size was not accurately measurable, whereas the muscle response had already become too small to measure, even with greatly increased amplification, above a stimulus strength of 30 volts.

To see if further information could be obtained about the afferent fibres concerned in the response to electrical stimulation the blood supply to a limb was cut off. A pneumatic cuff inflated to above the systolic blood pressure was applied to an upper arm in one experiment and to a thigh in another. After 25 to 35 minutes of ischæmia, when the conditions in the limb were changing rapidly, the interval that necessarily occurred between the examinations of sensory function and of the cerebral response to electrical stimuli made difficult correlation of the results of the two tests and the experiments were abandoned. In the two experiments made it seemed that the cerebral response to electrical stimulation of the nerve did not fail significantly before voluntary movement was lost in the muscles supplied by the nerve being stimulated. One interesting observation was made in the experiment where the cuff was applied to the right upper arm. After ten minutes of ischæmia it was noticed that the right foot was in a state of continuous slight clonic movement. This movement persisted until between two and three minutes after the circulation had been restored. At the end of the experiment the subject volunteered the information that his arm had felt for much of the time as though it had been bent up at the elbow and the fingers had been clenched. No record was available as to whether this sensation, which may have been the same as that of the "pseudo-cramp" described by Lewis, Pickering, and Rothschild (1931), began at the same time as the twitching in the right foot, but it may be suggested that possibly the twitching was caused by the discharge of afferent impulses which was giving the false sense of position.

Experiments were made to find if any cerebral response could be produced by stimulation of a sensory nerve containing no afferent fibres from muscle. When the stimulus was applied to a small cutaneous nerve and made strong enough to be painful no cerebral response was found to follow. Stimulation of the sural nerve at the external malleolus provoked a cerebral response, but the strength of the shock was such that it was difficult to avoid spread to muscles from the cathode and stimulation of muscles under the anode. No useful information was obtained concerning latencies in this case as it was not certain that the response was due to stimulation of the sural nerve or at what level stimulation was occurring.

Stimulus Frequency.—In the experiments so far described the rate of stimulation was maintained

at about once per second. This rate was chosen because the severe myoclonic jerkings disappeared after three or four stimuli and the first waves of the cerebral response did not seem to be altered in shape from those that followed a single stimulus. In some experiments where faster rates of stimulation were used for short periods it seemed that unusually severe myoclonic jerkings occurred. Experiments were therefore made to investigate the effect on the response of the stimulus frequency. At first the method used was to stimulate a nerve at a rate increasing steadily from once a second to fifty a second, and to take a continuous EEG record. The effect of such a series of stimuli is shown in the record in Fig. 12. At a rate of stimulation of 4·2 per second, Fig. 12A, it is difficult to pick out any response amongst the spontaneous activity from brain and scalp muscle in the record. As the stimulation rate increases oscillations with a period of a thirtieth of a second begin to appear in groups at intervals of half a second. At a stimulation rate of thirty per second, Fig. 12C, the myoclonic jerkings had become very violent and there are large groups of waves with a frequency of thirty per second separated by intervals of 350 to 400 msecs. This grouping tended to be maintained after the stimulation rate had been reduced to 12·5 per second, Fig. 12D, and is still visible with 5 stimuli per second. The critical frequency of stimulation at which the myoclonic jerkings became violent and at which the responses to the stimuli became clear in the record seemed to lie between 8 and 15 per second.

In another experiment, in which the rate of stimulation was changed more slowly in an attempt to find this critical frequency more accurately, the subject passed into a major convulsive seizure. Since such seizures were relatively rare the method was not used further and experiments were made using one conditioning stimulus followed at varying intervals by a test stimulus. The pair of shocks was applied once per second and their separation was varied between 10 and 350 msecs. At each interval fifty pairs of stimuli were applied and the records of the cerebral responses were superimposed; a series of records made in this way is shown in Fig. 13. The time scales show intervals of 5 and 20 msecs., and the black dots indicate the positions of the stimulus markers in the time scales and the positions of the stimulus artefacts in the records of the cerebral responses. The intervals between the stimuli are indicated at the left hand end of the records and an S indicates fifty single control stimuli. The size of the single stimulus necessary to produce a maximal cerebral response was found, and the first and second shocks in all the records were made twenty per cent. larger than this. The stimuli were applied to the right ulnar nerve at the wrist.

The responses to the second shock of a pair are reduced in size when the second stimulus follows the first by between 10 and 30 msecs. At intervals of 40 and 50 msecs. the response to the second shock is superimposed on the end of the response to the first shock, and it appears to be the same size as or slightly larger than the first response. From 60 to 100 msecs. the second response is increased in size by 50 to 70 per cent., the greatest increase being apparently at 60 to 70 msecs. Between 120 and 160 msecs. the second response is depressed in size. This depression is greatest at about 140 msecs., where it may be seen by comparison with the record below, showing the responses to fifty single control shocks at one second intervals, that the delay between the stimulus and the response is significantly increased and is more variable when the response is depressed. The reduction in size is greatest in the second, positive, phase of the response which also becomes more oscillatory. The first phase of the response has apparently returned to normal at intervals of 180 msecs. and longer, but the more oscillatory nature of the later part of the response persists with an interval between the stimuli up to 350 msecs. It is interesting to note that the period of facilitation between 60 and 100 msecs. corresponds to the frequency of tetanic stimulation at which the myoclonic jerkings began to become very severe and at which the large cerebral discharges began to appear in the record in Fig. 12. At this interval between the stimuli the subject also began to complain that they were unpleasant in character. The interval of 350 to 400 msecs. between the groups of discharges at the faster rates of stimulation in Fig. 12 apparently corresponds to the period necessary for recovery after a previous discharge, as shown by the records in Fig. 13.

Discussion

The evidence that the discharges detectable on the scalp following sensory stimulation are of cerebral origin lies first in the delay between the stimulation and the response and secondly in the distribution of the responses. As the point at which the stimulus was applied was moved farther towards the periphery the latency of the response increased, and the amount of the increase was consistent with the cause of the disturbance on the scalp being propagated along the nerve stimulated. Such an increase in latency would not be expected if the electrical change on the scalp was due to any direct electrical conduction of the stimulating current to the head. The short latency of 19 msecs. between a stimulus

applied at the elbow and the response on the head makes it unlikely that the response was a twitch of scalp muscle caused by the volley of impulses in the afferent fibres stimulated. That a twitch of scalp muscle was probably not the cause of the changes of potential detectable on the scalp is also suggested by the distribution of these potential differences which were maximal on the side opposite to that stimulated. The response to stimulation of a nerve in the leg was maximal near to the vertex, where the amount of muscle is least, and when stimulating a nerve in the arm it was maximal 6 to 8 cm. lateral to the midline. This distribution suggests strongly that the potential changes detectable on the scalp were originating in the primary sensory cortex where the limb stimulated is represented. The only point against this is that in all the experiments the activity provoked by the stimuli was found to have a maximum 3 to 4 cm. in front of the surface markings of the central sulcus. Though this difference is probably at the extreme limit of variation of the position of the central sulcus with respect to the surface markings, it may still be possible that these potential changes detectable on the scalp following sensory stimulation do represent cerebral activity from the region of the post-central sensory cortex.

The considerations discussed apply only to the first part of the response, and when it is followed by a wave of negativity at the active area, and a group of waves with a frequency of thirty per second accompanied by a generalized myoclonic jerking, it is difficult to define the distribution of these disturbances, though it seems that they spread more widely. The occurrence of such a clear local response associated with the stimulus, following as little as 19 msecs. after it when stimulating at the elbow, and also the relatively rapid rate of thirty per second of the later discharges, distinguishes this subject from those with myoclonic seizures previously described (Dawson, 1946). In these subjects, even during the times when sensory stimulation would provoke seizures, no similar local response was seen, and the rate of the later discharge lay between 8 and 14 per second. Whether or not this difference in the rates of discharge during the myoclonic seizures would account for the differences in the muscle action potentials in the two types of case is not clear. In the subject of the present experiments the muscle action potentials during the seizures were less simple than those in the cases described previously, where they were as brief and discrete as the action potentials during a reflex twitch from a tap on a tendon.

The first local response to stimulation in the subject of the present experiments bears in some ways a close resemblance to the responses which have been described in healthy subjects in similar conditions of stimulation and recording (Dawson, 1947). The latencies of the responses following stimulation of arm and leg correspond closely with those occurring in the healthy subjects and the distribution of the response is the same in the coronal plane, though in the healthy subjects the area of maximum activity in all cases where a response was found corresponded more closely with the surface markings of the central sulcus. No anatomical difference between the myoclonic subject and the healthy subjects, such as an atrophy of frontal cortex in the myoclonic subject, which might account for the difference was demonstrated radiologically. The polarity of the disturbances following stimulation in the present subject and in the healthy subjects previously described, where in the first phase of the response the active area became positive with respect to other parts, appears to be the same, though in no case was anything comparable to the negative change and the following spike discharge in the subject with myoclonus seen in the healthy subjects. The only major difference in the local responses in the myoclonic and healthy subjects is that in the myoclonic subject the potential difference on the scalp during the response was five to ten times as large as in the healthy subjects. If the condition producing these large initial responses in the patient with myoclonus is a general cortical one, it might be expected that the myoclonic jerkings would more often progress into a generalized tonic-clonic seizure, similar to that which occurred in the subjects with myoclonus previously described, but this rarely happens. The form of the discharge following stimulation of the lateral popliteal nerve, shown in Fig. 7A, corresponds closely with that of the responses following electrical stimulation of peripheral nerve in the monkey, recorded by Marshall, Woolsey, and Bard (1941) from exposed cortex after recovery from ether anæsthesia. This suggests, like the correspondence in the time course and polarity of the response with that in healthy subjects, that the initial discharge in the myoclonic subject is abnormal only in size and not in other qualities.

Marshall and others suggest that the discharge they described is associated with the arrival of the afferent volley at the sensory cortex. This suggestion is supported by the work of Forbes and Morison (1939), who showed that a similar wave could be recorded from the white matter under cortex following electrical stimulation of a peripheral nerve, and by the work of Adrian (1941) who showed that after complete removal of the sensory cortex a wave could be recorded from the white

matter leading up from the thalamus, following stimulation by touch, which was virtually identical with that which had been recorded from cortex before its removal. If in fact the initial wave in the response to stimulation in the myoclonic subject and in the healthy subjects is comparable with those described in animals by Forbes and Morison, by Adrian, and by Marshall and others, and if it is associated with arrival of the afferent volley at the cortex and not with any subsequent cortical activity, as is suggested by the short latency and the polarity of the first phase of the response, then the cause of the great difference in size between the responses in the healthy and the myoclonic subjects must be sought below the cortex, possibly at the level of thalamus. What light the changes in the size of the response to the second of a pair of shocks throw on the site of the facilitation that occurs at certain intervals between them is not clear, but it may be noted that the time of recovery after a discharge, 350 to 400 msecs., is closely similar to the period of the wave and spike discharges which appear synchronously on the two sides in the EEG during certain epileptic seizures. Jasper (1941 b) suggested that these discharges might be initiated from diencephalic structures, and more recently Fortuyn and Jasper (1947) have shown that a cortical discharge of wave and spike form may be elicited at a rate of three per second by stimulation of the dorso-medial nucleus of the thalamus in cats.

In clinical examination the only stimulus found adequate to provoke the myoclonic jerking was one involving stretching of a muscle. The tests of the threshold for electrical stimulation of peripheral nerve also suggested that the nerve fibres concerned in the response were more sensitive than the motor fibres in the nerve and had the same order of conduction velocity. The failure to find responses that were undoubtedly due to stimulation of sensory nerves containing no afferent fibres from muscle may have been due to the size of the shock used being insufficient to excite enough fibres. Bigger shocks became very painful and it was difficult to prevent stimulation of neighbouring muscles. If the fibres which could be stimulated to produce the cerebral response are in fact the large afferent fibres from muscle, the low order of conduction velocity in them obtained in these experiments, not higher than 60 to 80 metres per second, needs further consideration when it is compared with the figure of 116 metres per second described by Lloyd (1943). Figures of 45 metres per second have been obtained in healthy subjects for the conduction velocity in the motor fibres in the ulnar nerve and also for the afferent fibres in experiments on the reflex response to electrical stimulation of the type described by Hoffman (1922) It seems possible that the lower conduction velocity in the peripheral nerves in the limbs in man may in part at least be due to lower temperature, since Lloyd's figures were obtained in the cat presumably at 37° to 38° C., though the temperature is not specified, and it is known that in man the temperature in an unclothed limb at rest may fall considerably below this figure. The low conduction velocity in the afferent systems is not necessarily inconsistent with the clinical observations that the adequate stimulus for producing the jerkings was that of muscle stretch.

Summary

1. A subject is described in whom sensory stimulation in the form of stretching a muscle or electrical stimulation of peripheral nerve provokes myoclonic seizures.

2. Electrical disturbances in the EEG preceding and during the seizures are described. The first part of the potential change is largest on the side of the head opposite to the site of the stimulus and 3 cm. in front of the surface marking of the central sulcus. It is maximal near to the midline when stimulating the leg, and 6 to 8 cm. lateral to it when stimulating the arm.

3. The latency of the response on the scalp becomes greater when the stimulus is applied nearer to the periphery ; it varies from 19 msecs. stimulating at the elbow to 43 msecs. when the stimulus is applied at the ankle.

4. The response to the second of two stimuli is depressed if the second stimulus is applied within 30 msecs. of the first. The response is facilitated if the interval between the stimuli is from 60 to 100 msecs., it is depressed again following this, maximally at 140 msecs., and has recovered almost completely at 300 to 350 msecs.

5. It is concluded that these responses to stimulation are cerebral in origin.

6. Attempts to define the characters of the afferent systems concerned are described.

7. The findings are compared with those in healthy subjects. The responses to stimulation in the subject with myoclonus have a similar latency, form and time course to those in healthy subjects but they are between five and ten times as large.

8. The significance of the findings is discussed.

The author would like to express his gratitude to Dr. E. A. Carmichael, who joined in many of the experiments, for his constant advice and encouragement.

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ACTINOMYCOSIS OF THE BRAIN

BY

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(RECEIVED 8TH AUGUST, 1947)

THE following case of actinomycosis of the brain is described since it presents several interesting features, particularly the involvement of the sphenoid bone, a rare occurrence according to the literature, and the spread of the disease to the venous sinuses. The literature has been examined from these aspects and a summary added of cases of actinomycosis of the brain reported in the ten years following the extensive reviews of the subject by Friedman and Levy (1938) and Cope (1938).

Case Report

A corporal, aged 31 years, was first admitted to hospital on June 30, 1944, complaining of sudden onset of headache nine days previously, with fever for the last five. The only past illness was an attack of malaria in 1930. He looked ill, but nothing abnormal was found on clinical examination; there were 6,000 white blood cells per c.mm. of blood, and the sedimentation rate was 50 mm. in the first hour. He remained in hospital for a month, the symptoms persisting, and all investigations, including blood cultures and smears, sputum examination, lumbar puncture, blood Kahn, and radiographs of chest and sinuses proved negative. The only change noted on clinical examination was the development of a complete right sixth cranial nerve palsy on July 20.

The patient came under the authors' observation on July 28, when he was transferred to a neurosurgical unit for further investigation. Then he looked pale and ill, with temperature 100° F. and pulse 88 per minute. The headache was severe, mainly felt as a throbbing pain over the left side of the head; there was marked neck rigidity, but Kernig's sign was negative. Hirsuties over the body was very noticeable and he had obviously lost weight recently. Examination of the nervous system showed the right sixth nerve palsy, a little weakness of the left arm and left hip, and doubtful diminution of the lower left abdominal reflexes. All other systems were normal, and a full examination of the ears, nose, and throat, carried out by Lieut.-Col. R. B. Lumsden, R.A.M.C., was negative. A lumbar puncture showed a cerebrospinal fluid pressure of 110 mm. Queckenstedt responses were normal, protein 40 mg. per 100 c.cm., there were no cells, the Wassermann reaction was negative, and the Lange reaction 0000000000. A full *x*-ray study of the skull and cervical spine was normal; the sedimentation rate was now 100 mm. in the first hour, and the white blood count 11,000 per c.mm. of blood (81 per cent. polymorphs).

The fever continued rising to 102° F. in the evenings, and on Aug. 2 fresh signs of a partial right third nerve palsy developed. A course of sulphadiazine was begun on Aug. 6, after a further examination had revealed nothing new apart from a slight diminution of the reflexes in the left arm and leg. That same evening a complete *left* sixth nerve palsy developed. On Aug. 7 the patient complained of some tenderness in the right side of the neck and it was noted that the trachea was displaced a little to the left: on Aug. 10 he had pain in his right chest and a pleural rub was heard in the right axilla. By now the third nerve palsy had improved a little but the neck was held very stiffly and the patient was afraid to move it at all; the upper part of the right posterior triangle of the neck was swollen and tender, and it was thought that a hard mass could be felt beneath and behind the sternomastoid. Further radiographs of the chest and cervical spine were negative, as was another ear, nose, and throat examination.

On Aug. 17 the neck was examined under general anæsthesia. Nothing abnormal was felt, the supposed mass being presumably due to muscle spasm. A 3-inch incision was then made along the posterior border of the sternomastoid extending down from the mastoid tip; exploration in all directions and down to the transverse processes revealed no abnormality and the wound was closed. Sulphadiazine was now discontinued, after the patient had had 113 g. without effect on the condition apart from some lowering of the temperature. A blood transfusion of three pints was given on Aug. 27. At this stage, therefore, no definite diagnosis had been reached; the clinical picture suggested an infiltrating lesion at the base of the skull, but whether infective or possibly neoplastic from a small primary in the nasopharynx could not be determined.

At the beginning of September an attack of amœbic dysentery declared itself, for which the patient received a course of emetine. It was interesting to observe that, in addition to its local effect, the emetine seemed to improve the patient's general condition, his neck becoming less stiff and his temperature subsiding.

The signs in the central nervous system remained unchanged, and on Sept. 26 ventriculography was

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performed. The cerebrospinal fluid from the right ventricle was slightly blood-stained (protein 40 mg. per 100 c.cm., red blood cells 6,240 per c.mm., white blood cells (lymphocytes) 3 per c.mm. ; the fluid from the left showed 20 mg. protein per 100 c.mm. and white blood cells (lymphocytes) 4 per c.mm. The ventriculograms were normal, but it was seen that compared with the radiographs of seven weeks previously there was now destruction of the posterior clinoid processes, erosion of the dorsum sellæ, and opacity of the sphenoidal sinuses.

A few days later a mass began to develop beneath the previous operative scar in the neck, and by Oct. 13 it was obviously fluctuant. Aspiration yielded 25 c.cm. of thick, creamy, offensive pus which on full bacteriological examination showed Gram-positive cocci and short Gram-positive bacilli in the films, and non-hæmolytic *Staphylococcus aureus* on culture aerobically and anaerobically. The blood sedimentation rate had risen to 144 mm. per hour ; the white blood count was 8,800 per c.mm. A diagnosis of osteomyelitis of the base of the skull secondary to sphenoidal sinus infection was made, and on Oct. 21 a sphenoidal canula was passed into each sinus. The left return was clear, but opalescent fluid was obtained from the right side which on culture grew *B. subtilis* and a non-hæmolytic streptococcus. This latter organism, and the staphylococcus grown from the neck abscess, were both penicillin-sensitive, and an intramuscular course of 1,320,000 units of penicillin was given from Oct. 23 to Nov. 3. After this treatment, washings from the sphenoidal sinus grew *B. coli* only : the neck had become less rigid, no mass could be felt, and the scar was sound. A further blood transfusion of two pints was given.

On Nov. 8, the patient suddenly developed a series of generalized epileptic fits which were controlled by phenobarbital. An intracranial abscess was suspected and the ventriculogram repeated. The right ventricle was not found, but the left was entered easily and a radiograph showed it to be normal in size and position. The cerebrospinal fluid from this side showed a raised protein of 70 mg. per 100 c.cm., red blood cells 675 per c.mm., and white blood cells 15 per c.mm. (88 per cent. lymphocytes, 12 per cent. polymorphs). Over the next few days the patient's condition deteriorated ; he became mute, and the left-sided weakness progressed to a complete hemiplegia with bilateral papillœdema. He died on Dec. 5, just over five months after the onset of symptoms.

Eight lumbar punctures were performed during his illness and, with the exception of the last cerebrospinal fluid, all had normal protein, cell, and chloride contents ; the Queckenstedt responses were normal, and the cerebrospinal fluid pressures within normal limits. The last puncture, done on Nov. 25, showed a cerebrospinal fluid pressure of 300 mm. with 80 mg. per 100 c.cm. protein, 10 lymphocytes per c.mm., chlorides 800 mg. per 100 c.cm., and normal sugar.

Autopsy

Head.—The posterior third of the superior longitudinal sinus was distended and occluded by a soft, purulent thrombus, extending to the torcular Herophili and continued into the right lateral sinus, where the periphery of the clot was undergoing organization, though bearing signs of previous infection. This clot ultimately merged into a thick white cord of fibrous tissue, filling the right sigmoid sinus without adhering to its walls, and reaching as far as the jugular bulb. The right superior petrosal sinus was similarly occluded by organized thrombus : the right inferior petrosal and straight sinuses, and the sinuses on the left side were healthy.

The pituitary gland was embedded in a mass of fibrous tissue riddled with tiny yellow spots and obliterating the right cavernous sinus. When this was stripped away, the floor of the sella turcica was seen to be severely eroded, with a worm-eaten appearance, and in the centre of the floor was a rounded pit 8 mm. in diameter and 8 mm. in depth, oozing with thin greenish-yellow pus. This hole did not communicate visibly with the naso-pharynx or sphenoidal air-sinus. The posterior clinoid processes were eaten away completely, and the whole basi-sphenoid bone was bright red and roughened with osteomyelitis, thin pus welling up through the lacunæ to its upper surface (Fig. 1, p. 166). The ethmoidal and sphenoidal air-spaces contained a little muco-pus : the frontal sinuses and maxillary antra were clear : the middle ears and mastoid processes were normal.

Yellow nodules similar to those around the pituitary were present in the soft tissues surrounding the right atlanto-occipital joint, and extended into the right hypoglossal canal. The right atlanto-occipital joint showed signs of previous infective arthritis, with thickening and opacity of the synovial layer. It was not possible to trace any visible connexion between these lesions and the nasopharynx, nor to demonstrate a primary focus in the nasopharynx or buccal cavity.

The dura mater was densely adherent over the parieto-occipital aspect of the right cerebral hemisphere, and beneath it lay a subacute subdural empyema, loculated by adhesions. After the slimy greenish-yellow pus was washed away, numerous broad and deep pressure-indentations up to 15 mm. in depth were observed in the cortex. The pus extended down into the right Sylvian fissure and the under-surface of the right frontal lobe and uncinate fissure. The pons was flattened by intracranial pressure, but the anterior surface of the brain stem was not grossly infected. The cerebral convolutions on the left side were markedly flattened by pressure.

The whole of the right temporal lobe was bulkier than the left, and the posterior part of its under-surface was gummed to the tentorium cerebelli. On this being stripped away, a broad yellow area was revealed, midway between the temporal and occipital poles, and extending from the right crus laterally for 6 cm. Section of the brain showed this yellow plaque to be the inferior wall of a subpial abscess 12 mm. in depth, of fairly recent origin, and more acute than the subdural empyema. The white matter of the adjoining right temporal lobe was grossly swollen by œdema, causing medial displacement and undue exposure of the right hippocampus, while the cavity of the inferior ventricular horn was reduced to a mere slit (Fig. 2, p. 166). There was no evidence of ventriculitis, however, and the rest of the ventricular system was normal in appearance.

HISTOLOGY

Right cavernous sinus.—The blood spaces were replaced by a mass of granulation tissue, in parts breaking down into small abscesses. In the centre of some of these were colonies of *S. actinomyces* (Fig. 3, p. 167). The wall of the carotid artery at this level was intact.

Right temporal lobe.—The abscess lay between the surface of the cortical grey matter and the pia-arachnoid ; in the pus lining its walls were colonies of *S. actinomyces* (Fig. 4).

BACTERIOLOGY.—Direct smears of the subdural pus showed a rich mixed flora-streptococci in chains, staphylococci, gram-negative diplobacilli, diphtheroids, and scanty fine filaments with metachromatic granules. On culture, *Staphylococcus aureus* and hæmolytic streptococci were grown aerobically, coliform bacilli and diphtheroids anaerobically. Culture on Saboraud's medium yielded a growth of long branching gram-positive filaments, morphologically *S. actinomyces*.

Thorax.—The heart was normal. The right lung contained several small abscesses, of a fairly chronic nature. In each lung were scattered a few smooth-walled cysts, apparently of congenital origin.

HISTOLOGY.—Some of the lung abscesses were acute, associated with hæmorrhage, and obviously embolic in origin ; the more recent, on gram-staining, showed a mixed bacterial flora. Others however, were surrounded by granulation tissue, or even dense fibrosis with numerous giant cells, and were weeks or months old. In one of these a colony of *S. actinomyces* was found (Fig. 5).

Abdomen.—The spleen was enlarged and congested. The colon contained a few amœbic ulcers. The other organs were normal.

SUMMARY AND DIAGNOSIS

The chronicity of the lesions suggests that the infection was actinomycotic from the outset. After infection of the basisphenoid bone, spread occurred to the soft tissues around the sella turcica, with involvement of the right cavernous sinus, progressive thrombosis along the superior petrosal and right lateral sinuses, and recurrent metastatic abscesses of the lungs. Infection of the meninges resulted in a subdural empyema and subpial abscess. The congenital cysts of the lungs and the amœbic dysentery were coincidental lesions.

Comment

This case illustrates several clinical characteristics of actinomycosis. The long course of the disease, the temporary improvements with actual remission of clinical signs in the nervous system, is well exemplified here as is the difficulty of diagnosis and of isolating the causal agent even when suspected, the picture being apparently dominated by the secondary pyogenic invaders which are mainly responsible for toxicity of the disease process.

The spread of the infection from the basisphenoid to the atlanto-occipital joint accounted for the pronounced neck symptoms and signs, and a septic embolism to the lung was responsible for the attack of pleuritic pain. The marked signs in the central nervous system which developed in the last days were presumably due to the extension of the subdural empyema. The findings on lumbar puncture were very interesting : despite the extensive intracranial infection the spinal fluid remained normal in all respects, with the exception of the last examination ten days before death, which showed only a slight increase of protein and cells. It should also be noted that the Queckenstedt response on the right side remained normal despite the presence of organized thrombus in the transverse sinus on that side : the absence of adhesions between the thrombus and the sinus wall, however, suggests that occlusion to blood-flow was not complete.

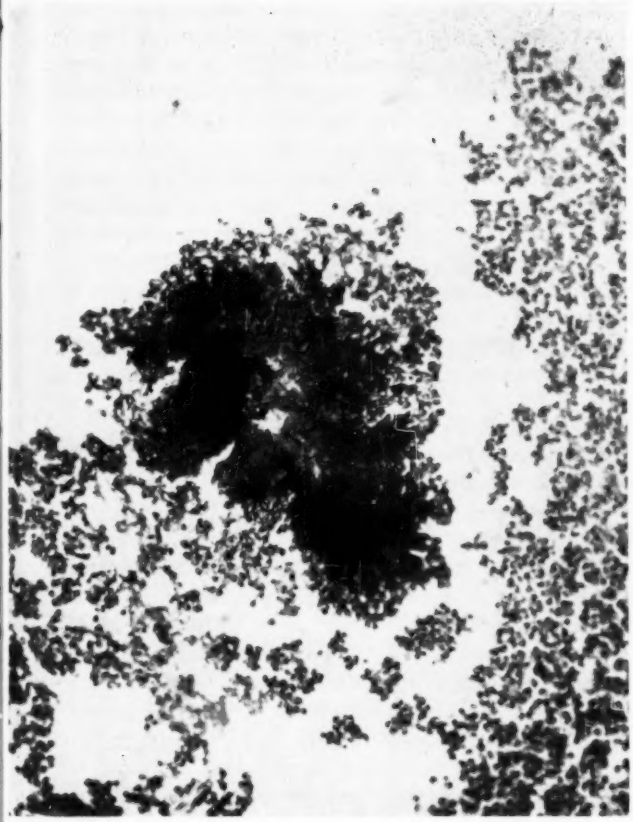
The marked changes in the sphenoid bone and the venous sinuses require further comment.

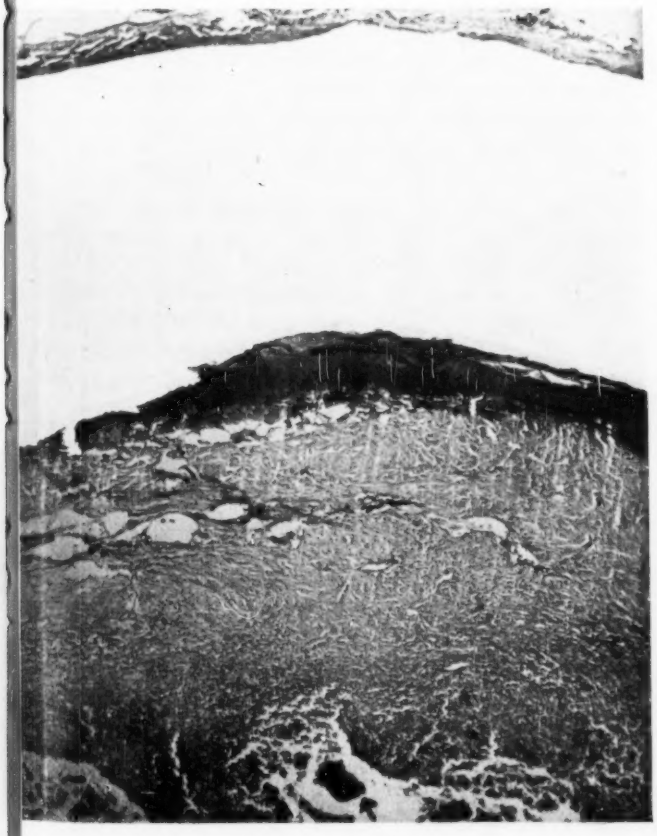
The sphenoid bone may be secondarily eroded as a result of intracranial invasion of actinomycosis from neighbouring structures such as the jaws, but primary infection of the bone is rare, and reports of only three previous cases could be found in the literature. Beevor and Buzzard (1903), Stevenson and Adair-Dighton (1911), and Kramer and Som (1935), each described a case of extensive osteomyelitis of the bone with meningitis and changes in the cerebrospinal fluid. Kramer and Som's case was similar to the one reported here in that a sphenoid infection had been diagnosed during life, but *S. actinomyces* was not detected in the sphenoidal washings, and at autopsy no obvious communication could be traced between the meninges and the sinus. In their case, however, serial sections demonstrated a sub-epithelial actinomycotic abscess in the wall of the left sphenoid sinus and colonies in the marrow spaces of the bone and in the thickened dura covering the basisphenoid. No other focus was found in the buccal cavity or nasopharynx of these cases ; and they, together with the one described here, are considered primary sphenoid infections. This does not exclude the possibility that there may have been a focus elsewhere in this region at a previous date, since, as pointed out several times before, the spread of actinomycosis is characterized by healing of the track behind the advancing lesion.

The involvement of the intracranial venous sinuses was an important feature of the case reported here. The predilection of actinomycosis for the region of the sella turcica, whether by direct extension or metastasis, is well known, and several case reports draw attention to collections of pus or granulomatous masses around the pituitary region, and some to abscesses within the gland itself. The descriptions

FIG. 1 (left).—Osteomyelitis of basisphenoid. Note the extensive erosion and the organized thrombus in the right lateral sinus.

FIG. 2 (above).—Right temporal sub-pial abscess with surrounding œdema.





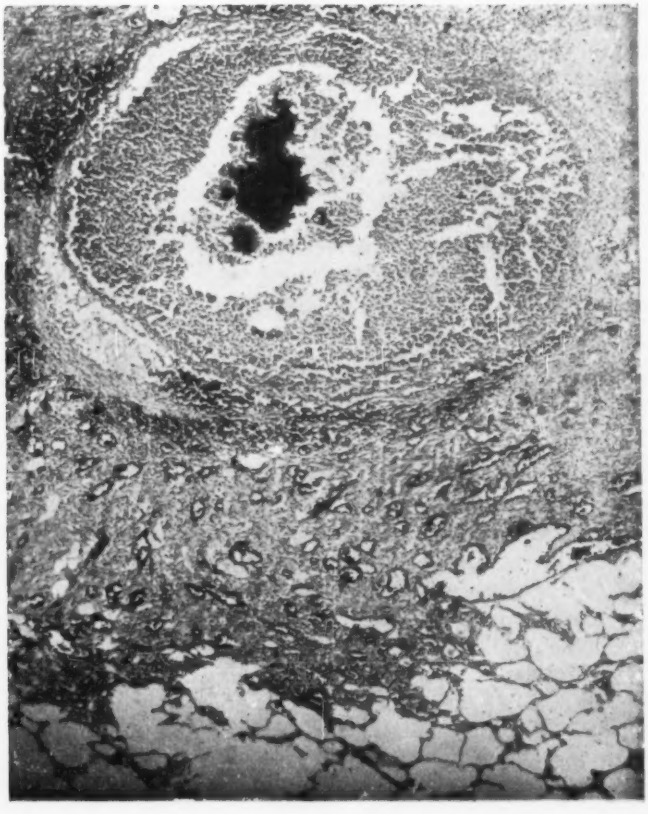


FIG. 3 (top left).—Section through the right cavernous sinus. The carotid artery is cut longitudinally. The arrow marks a colony of *S. actinomyces* lying within a small abscess, x 30.

FIG. 4 (top right).—*S. actinomyces* in wall of sub-pial abscess, x 140.

FIG. 5 (lower left).—Embolic abscess in right lung. Note the chronic inflammatory thickening of the abscess wall, x 30.

would suggest that the cavernous sinus was involved in several instances, but thrombosis of the venous sinuses has received scant attention in the literature, only six references to this complication being found.

In Ponfick's (1882) second case, the cavernous sinus was filled with pus and the left transverse sinus occupied by a gelatinous mass which was continued through the bulb into the left jugular vein with thrombosis of adjacent neck veins. Moosbrugger (1886) described the findings in a man of 27 whose primary focus was in the upper jaw : at autopsy the right transverse sinus contained a whitish purulent clot. Horn (1913) described a very unusual case of an otitis media due to actinomycosis. His patient developed meningitis and signs of a cavernous sinus thrombosis. A right mastoid exploration was done and the sigmoid sinus found filled with yellow debris ; the thrombosis extended backwards to the region of the torcular and down into the internal jugular vein which, at the operation, was ligated just above the clavicle and excised. At autopsy there was a purulent meningitis, pus in both orbits, and septic thrombosis of the right sigmoid sinus and jugular vein, both transverse sinuses, the posterior part of the longitudinal sinus, and both cavernous sinuses. Bell's (1922) patient had an acute meningitis with death in fourteen days : at autopsy a basal meningitis was found, the pituitary surrounded by pus and both cavernous sinuses filled with pus from which the fungus was grown. The case described by Friedman and Levy (1937) had yellow pus in the left cavernous sinus and coagulated bloody material in the longitudinal sinus ; the tissues around the pituitary were softened and four abscesses were found in the anterior lobe of the gland. Gonzalez Torres (1939) re-examined a museum specimen with meningitis and a mass of actinomycotic granulation tissue in the left middle fossa involving the Gasserian ganglion and the pons ; there were extensive thromboses of the venous sinuses including the superior longitudinal sinus and the left sigmoid sinus.

Bearing in mind the chronic nature of the infection, the cavernous sinus may be thrombosed without producing the classical signs of this complication—collateral channels can be used or only a partial thrombosis of the sinus occur as in this case. The discrete abscesses in the pituitary gland described in some cases may have followed retrograde thrombosis from the cavernous sinus. In this connexion it may be observed that in Turner and Reynolds' (1931) study of 21 cases of septic thrombosis of the cavernous sinus due to the common pyogenic bacteria, secondary involvement of the pituitary gland was found in four.

Not only may these thromboses be an important factor in the intracranial spread of the infection, but actinomycotic metastatic abscesses in the lungs may arise. They were present in the case reported here, and in the case described by Bell (1922). Multiple lung abscesses were also found in Kramer and Som's case although only gram-positive cocci were seen in the sections, and actinomycotic pulmonary abscesses were present in the case reported by MacFee (1932), where a basal meningitis followed actinomycosis of the jaw. No mention is made in these latter two cases of the condition of the venous sinuses, but the lung abscesses were presumably due to venous embolism.

Summary of the Literature

Extensive reviews of the literature of actinomycosis of the nervous system up to 1937 have been made by Friedman and Levy (1937), who found 108 cases recorded and listed seventy-six references, and by Cope (1938), who gave eighty-five special references and two additional ones in his general list, and divided them as far as possible according to the mode of invasion. Five additional references to cases recorded over this period, which do not appear in the lists of these authors, may be added. The case described by Beevor and Buzzard (1903) has already been mentioned : Letulle and others (1911) recorded a case of pleuro-pulmonary actinomycosis with a cerebral abscess which ruptured into the ventricle ; Belkowski (1911) a case of chronic pachymeningitis giving rise to several abscesses in the neck and diabetes insipidus ; Topley (1912) a basal meningitis with multiple cerebral abscesses following a primary focus in the abdomen—probably the appendix ; and Klemmer's (1923) second case was that of a young man with actinomycosis of the lung who over a period of eight years developed several metastases and finally succumbed to a cerebral abscess.

Over the last ten years, reports of twelve further cases have been found and are included in the following summary of the modes of invasion of the nervous system by the fungus. This may occur by one of three routes.

Primary.—With increasing knowledge of the disease it is apparent that several of the so-called primary cases hitherto reported were secondary to foci elsewhere in the body, the original lesion healing completely, or being discoverable only after diligent search. Although some authors deny that the infection can ever be primary in the nervous system, there is a small group of cases which can be classified as such. Cope (1938) drew attention to six cases in the literature where a so-called actinomycoma was discovered in the region of the third

ventricle, no other focus being found. Since then Orr (1945) has added one further case to this group. Macroscopically the appearance is that of a gelatinous tumour-like mass, firm in consistency, varying in size up to about one inch in diameter, situated in the third ventricle. It is clearly defined from the surrounding tissues and, as in Orr's case, may be pedunculated and produce the syndrome of intermittent obstruction usually associated with colloid cysts of that region. Microscopically, mycelial strands are recognized within degenerate cell masses lying in a gelatinous matrix. It is suggested that the portal of entry may be via the perineural spaces of the olfactory nerves.

Direct extension.—The disease may spread by extension from neighbouring parts from lesions in the paranasal sinuses, ear, pharynx, face, and jaws, and give rise to a basal meningitis which may be associated with cortical abscesses. The spread is usually along connective-tissue planes, entrance to the cranial fossæ being gained through the various foraminæ. There are, however, cases on record where undoubtedly direct spread through the bone has occurred, as in the case reported here. Friedman and Levy (1937) found twenty-three cases on record of spread by direct extension. Since that date Eckoff (1941) has described two cases of direct extension from the jaws. Harley and Wedding (1946) reported a remarkable case of a young soldier aged 19 years who had chronic sinusitis and developed a bilateral uveitis associated with alopecia, poliosis, and dysacousia, an unusual but previously described syndrome. In addition, he had symptoms of meningoencephalitis with a mild lymphocytic reaction in the cerebrospinal fluid. *S. actinomyces* was recovered from the spinal fluid and the aqueous humour.

Metastatic.—Most commonly the disease reaches the cranium through the blood stream from other foci in the body, particularly the lungs, and gives rise to cerebral abscesses, or meningitis (again usually basal), or both. Of the 108 cases of actinomycosis of the nervous system which they collected from the literature, Friedman and Levy ascribed sixty-two to this group.

Eight more cases belonging to this group have been reported in the last ten years. Zeitlin and Lichtenstein (1937) have recorded a case of basal meningitis and frontal abscesses (one of which had ruptured into the ventricle) from a lung primary: Morrison and others (1938) described a ventriculitis and basal meningitis following primary actinomycosis of a finger, a small abscess in the right lung being found at autopsy: and Burgstein (1940) a case of meningitis secondary to a lung lesion. Kulkov (1942) reported a left subdural empyema in a young woman which followed a primary lesion in the cheek and numerous sinuses over the body, an area of consolidation of the right upper lung being disclosed at autopsy: and Kasten (1945) described a case of basal meningitis and multiple frontal lobe abscesses following a lung primary, there being an additional lesion in the left kidney, the symptoms of which first brought the patient under observation.

Gonsalez Torres (1939) has made a histopathological study of two museum specimens of cerebral actinomycosis, one with cerebral abscesses and the other a granuloma of the middle fossa involving the left Gasserian ganglion and the pons with meningitis; the origin of the infection in these two cases was not stated. Similarly Aranovich (1942) reported an embolic hæmorrhagic meningoencephalitis but the post-mortem was limited to the head.

Summary

1. A case of actinomycosis of the sphenoid bone with involvement of the intracranial venous sinuses and development of a subdural empyema, subpial abscesses, and embolic abscesses in the lungs is described.

2. Three previous cases of sphenoid osteomyelitis have been recorded, and six autopsy reports describing involvement of the intracranial venous sinuses in actinomycosis of the nervous system have been found in the literature.

3. The ways in which actinomycosis may spread intracranially are summarized, and references to twelve fresh cases reported over the last ten years are added.

Our thanks are due to Cpl. Woods, R.A.M.C., for the photographs, and to Professor R. J. V. Pulvertaft and the Department of Medical Photography, Westminster Hospital, for the photomicrographs. The Director General of the Army Medical Services has given permission to publish this case.

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ARSENICAL ENCEPHALOPATHY IN INDIAN TROOPS

BY

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Introduction

UNTOWARD effects of antisyphilitic treatment, described as " arsenical encephalopathy," have been observed ever since trivalent arsenical compounds have been in use for the treatment of syphilis. Paul Ehrlich as early as 1914 believed the essential cause of the condition to be a dilatation of the small blood vessels of the brain which is followed by œdema and perivascular bleeding. He believes that the vascular change was due to some derivative of arsphenamine formed inside the body, as is suggested by the delay of several days before the characteristic reaction took place. Non-hæmorrhagic cases with necrosis and softening were described by Pollack and Riehl (1930). Demyelinating lesions were found by Dorothy Russell (1937). A comprehensive survey of the literature was made by Glaser and Imerman (1935). The condition has also occurred when the trivalent arsenicals have been used in conditions other than syphilis.

During 1943 and 1944 there were many fatalities among Indian troops undergoing treatment of syphilis with arsenicals. At the Third Medical Division's Conference, Southern Army, Poona, 1944, Krainer reported seventeen cases under the heading " arsenical encephalopathy."

In view of this high incidence an attempt was made to outline and classify the clinical picture and pathology of this condition with special reference to factors responsible for its appearance among Indian personnel. Reports of 184 cases were received from all over India. These included 37 cases observed in the Indian Military Hospital, Dunkirk.

Analysis of Material

An analysis of available case histories led to the following conclusions :

1. The incidence of arsenical encephalopathy in Indian troops is higher than the incidence rate of classical hæmorrhagic encephalopathy.

2. The incidence of this condition in Indian troops treated with *weekly injections* of N.A.B. is of the same order as the incidence in Indian civilians.

3. The increased incidence rate of this condition observed since 1943 is essentially the effect of treatment with *bi-weekly*, as opposed to the old standard treatment with *weekly* injections. (The dosage of arsenicals in the two treatment groups was uniformly standardized. Patients weighing 115 lb. and above received alternating 0·3 and 0·45 g. of N.A.B. Patients below 115 lb. received 0·3 g. per injection.)

4. The increased incidence after bi-weekly injections refers to Madrassis and Mahrattas only, the incidence in other provincial groups showing no significant increase. It is noteworthy that the incidence rate is higher in the two provincial groups with the lower average body weight.

5. Malaria during or immediately before antisyphilitic treatment is an important factor in increasing the rate of arsenical encephalopathy.

Statistics.—The reported incidence of arsenical encephalopathy in the Army in India from August, 1943, to March, 1945, was :

Indian cases	181
British cases	3

The Indian cases were distributed as follows :

Madrassis	97
Mahrattas	22
Others	62
	181

Table I shows the total number of cases undergoing antisyphilitic treatment, and the incidence of arsenical encephalopathy, in the Indian Military Hospital, Dunkirk, and the Indian Military Hospital, Jalahalli. The average incidence rate in these groups is far higher than that recorded in the literature, for example, 0·2 per thousand in Glaser and Imerman's statistics. Statistics from the Madras General Hospital (1,000 cases treated with neoarsphenamines : Rajam and Rao, 1939) show a rate of 0·5 per cent., that is, twenty-five times Glaser and Imerman's figure.

Table II shows the incidence of arsenical encephalopathy classified according to weekly and bi-weekly injections. It shows that the incidence rate of arsenical encephalopathy is not due to a proportional increase in all groups. The incidence is six times the incidence following weekly injections in Madrassis and four times in Mahrattas, but it is only 0·2 per cent. higher in Indians from other provinces, which is below statistical significance.

TABLE I

Provincial group	Syphilis under AST	Cases of arsenical encephalopathy	Incidence %
I.M.H. Dunkirk			
Madrassis ..	657	14	2·1
Mahrattas ..	460	16	3·5
Others ..	792	7	0·9
Total ..	1,909	37	1·9
I.M.H. Jalahalli			
Madrassis ..	1,548	31	2·0
Others ..	820	8	1·0
Mahrattas (not separately recorded)			
Total ..	2,368	39	1·6

Comparison of figures for the Indian Military Hospital, Dunkirk, and the Indian Military Hospital, Jalahalli, from January, 1944, to March, 1945.

The average weight of Madrassis and Mahrattas is below that of the group classified as "Others" (see Table III).

Social Incidence.—Of the patients under antisyphilitic treatment, 11·1 per cent. (212 out of 1,909 cases) were non-commissioned officers; only three of these developed arsenical encephalopathy. No case was recorded in a Viceroy-commissioned officer or gazetted Indian officer. It was considered that at least part of the high racial incidence in Indians is social incidence. It seems a reasonable conjecture that a deficient diet plays a part. Lydon (1944) has stressed the possible relationship of Vitamin B_1 and C deficiency. The poor Madrassi diet is known for its deficiencies (McCarrison, 1921).

Malaria.—Thirteen cases out of a series of 1,909 developed benign tertian malaria during or shortly before undergoing antisyphilitic treatment; of these, four developed arsenical encephalopathy, giving an incidence of 30·8 per cent. as against 1·9 per cent.

Time of Onset of Arsenical Encephalopathy.—The intervals between the first injection of N.A.B. and the onset of arsenical encephalopathy can be seen in graphs 1, 2, 3, and 4.

The influence of the stage of the syphilitic infection on the incidence rate of arsenical encephalopathy is shown in Table IV, from which it can be seen that the incidence of arsenical encephalopathy in sero-positive primary and secondary syphilis is no higher than in sero-negative primary syphilis. On the contrary, the incidence rate in sero-negative primary syphilis is higher than in the other two groups of this series, the difference being below statistical significance.

Mortality Rate.—The mortality rate is shown in Table V. The mortality rate of arsenical encephalopathy was 76 per cent. in the series of Glaser and Imerman; it will be seen, therefore, that the mortality rate is lower in Indian troops, but the fatalities from encephalopathy in Indian troops are 75·9 per cent. of all fatalities during antisyphilitic treatment, as against 50 per cent. in the series of Cole and others (1931).

The Clinical Picture

This description is based upon the analysis of 37 cases observed in the Indian Military Hospital, Dunkirk. In general a fairly definite sequence of events could be outlined.

Prodromal Symptoms.—In a few cases, several days before the onset the patient exhibited headache, fever with a negative blood slide, and malaise. This was often associated with excessive thirst, a feeling of chilliness and exhaustion, and, on occasion, abdominal colic and epigastric tenderness. These became enough to warn us that encephalopathy threatened.

Onset.—Gradual and sudden types occurred in approximately equal numbers; the latter commenced as an epileptic fit followed by evidence of cerebral irritation.

Progress.—For the purpose of description four subsequent stages may be distinguished. For the sake of convenience they may be called, somewhat arbitrarily, stage one, two, three, and coma. A patient may never progress beyond stage one or stage two.

The essential feature of stage one is that the patient, though mentally retarded, is still accessible and is able to walk about. He may complain of malaise and lethargy, and often of fear; visual hallucinations and confusion may be prominent. He tends to wander from his bed. On examination the pupils are found to be

TABLE II

Frequency of injections	No. of cases of AST				Number of A.E.				Incidence rate %			
	Madrassis	Mahrattas	Others	Total	Madrassis	Mahrattas	Others	Total	Madrassis	Mahrattas	Others	Total
Weekly	342	173	380	895	2	2	3	7	0·6	1·2	0·8	0·8
Bi-weekly	315	287	412	1014	12	14	4	30	3·8	4·9	1·0	3·0

Incidence of arsenical encephalopathy classified according to frequency of injections.

TABLE III

Provincial group	No. of cases	Weight (lb.)	
		Average	Range
Madrassis under AST ..	657	99	78–148
Madrassis A.E.	14	103	95–120
Mahrattas under AST ..	460	103	83–141
Mahrattas A.E.	16	92	90–110
"Others" under AST ..	792	108	97–157
"Others' A.E.	7	114	100–120

Classification of cases under antisyphilitic treatment and cases of arsenical encephalopathy, according to provincial group and body weight.

TABLE IV

Stage of syphilis	No. of cases of A.S.T.		A.E. No.	A.E. %
	Weekly	Bi-weekly		
Sero-negative primary	166	176	10	2·9
Sero-positive primary	495	561	15	1·4
Secondary	234	277	12	2·3

The influence of the stage of the syphilitic infection on the incidence rate of arsenical encephalopathy.

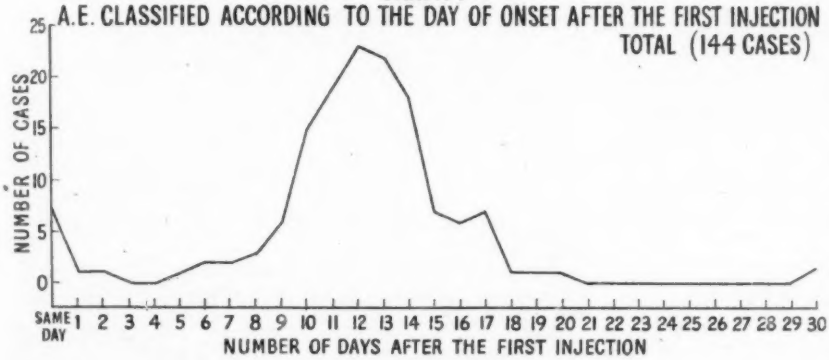
small and to react to light. There may be a general hyperæsthesia, but plantar reflexes and deep reflexes are normal while the abdominals may be absent. Questions are answered correctly, but there is a noticeable delay.

In the second stage the patient is more drowsy but can be roused. He is, however, unco-operative and resists examination. There is often hyperæsthesia and fever. Examination reveals small irregular pupils reacting to light. The deep reflexes are increased with unsustained ankle clonus. The superficial reflexes are lost and there is an upgoing toe.

The third stage is always pyrexial with increased respiratory rate, stertor, hiccough, and loss of sphincter control. There are frequent fits resembling status epilepticus. There may be teeth-grinding, moaning, etc. Examination shows dilated pupils reacting sluggishly to light, later becoming fixed. The deep reflexes and the swallowing reflex are still present. Kernig's and Babinski's sign may be present.

This is followed by deep coma in which the respiratory rate may exceed sixty per minute. The deep reflexes are lost. The pupils are fixed, and there is a tendency to hyperpyrexia. Every case which reached this stage died.

GRAPH I


A.E. CLASSIFIED ACCORDING TO THE DAY OF ONSET AFTER THE FIRST INJECTION
TOTAL (144 CASES)
NUMBER OF CASES
25
20
15
10
5
0
SAME DAY
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
NUMBER OF DAYS AFTER THE FIRST INJECTION

Special Examinations.—Examination of the fundus in ten cases showed no abnormalities, and blood pressure was within normal limits, the average being 117/73 mm. Hg. In ten cases that had reached stage three the cerebrospinal fluid pressure varied from 45 to 190 mm. water, the average being 87. The cerebrospinal fluid cell count ranged from 0 to 40, being under 4 in 32 cases, from 5 to 10 in 3 cases, and 11 and above in 2 cases. The total protein ranged from 70 to 900 mg. per 100 c.cm., average 207 mg. It was noted that no case with over 300 mg. per 100 c.cm. survived.

The cerebrospinal fluid Wassermann reaction was negative in 17 cases and positive in 3.

The white cell count ranged from 5,000 to 21,000 per c.mm.

Albuminuria was present in 12 out of 37 cases.

Treatment

Treatment consisted of general nursing and a standard treatment as recommended by Army Directive, which included: venesection, lumbar puncture, adrenaline, morphia, atropine, and the routine use of intravenous calcium gluconate. The results of this treatment as well as of additional procedures—administration of sodium thiosulphate and oxygen, were inconclusive. Case records illustrative of the types of cases encountered are appended.

Case Reports

Case 1.—A Madrassi Havildar (Sergeant), aged 19 years, weight 90 lb., was admitted to hospital on Sept. 17, 1944, with a generalized papular rash of 8 days' duration and a sore in the right inguinal region. Blood Wassermann and Kahn reactions were negative. He received four injections of N.A.B. bi-weekly, to a total of 1·2 g.

On Oct. 13, eleven days after the first injection he was apprehensive, restless, and groaning, but conscious and able to answer questions. He was incontinent of urine. The temperature was 98·4° F., the pulse rate 84, and the respiration rate 26 per minute. Babinski's sign was negative. By Oct. 14 he was dazed, refused to speak, and made occasional twitching movements with the

TABLE V

Complications of AST	No. of cases	Fatal cases	Fatality rate %
A.E.	37	20	54·1
Other than A.E. ..	49	6	12·2

Mortality

fingers. The left pupil was larger than the right, both reacting to light; there was bilateral nystagmus. The deep reflexes were present, and the plantar reflexes extensor. He was still incontinent of urine. The cerebrospinal fluid protein was 100 mg. per 100 c.cm.

By Oct. 16 the patient had recovered. This was a mild case, with fear as an early symptom.

Case 2.—A Madrassi Sepoy, aged 22 years, weight 95 lb., who had had a penile sore one year previously and now had a scar from the old chancre, and whose blood Wassermann and Kahn reactions were positive, was given four injections of N.A.B. bi-weekly, totalling 1·2 g. On Sept. 12, 1944, twelve days after the first injection, he suddenly fell while on fatigue. He was unconscious, and had hæmetemesis. The temperature was 100·2° F., and he frothed at the mouth. There were choreoid movements of limbs and head, and athetosis of the hands. The eyes showed conjugate deviation to the left. The pupils were moderately dilated and equal, and reacted to light. Babinski's reflex was negative. The deep reflexes were sluggish, and the abdominal reflexes absent. The right plantar reflex was extensor, the left equivocal. There was incontinence of urine. The cerebrospinal fluid pressure was 70 mm. water, five cells, protein 100 mg. per 100 c.cm.

On Sept. 13 the patient was grinding his teeth and had occasional convulsions. On Sept. 15 he was conscious and responded to questions, but with some delay. Abdominal reflexes were absent and plantar reflexes flexor; he was incontinent of urine on this day and the next, but by Sept. 19 he felt well.

This was a typical case with sudden onset.

Case 3.—A Sepoy, aged 36, weight 120 lb., classified as "Others," was admitted to hospital on June 4, 1944, with inguinal bubo. Routine blood Wassermann and Kahn examinations were positive. He received five injections of N.A.B. at weekly intervals, total 1·8 g.

On July 6, seventeen days after the first injection, he was found wandering aimlessly and was conducted back to the ward. The next day he looked vacant and was unable to reply to questions; five hours later he was found unconscious. The temperature was 102° F., the respiration rate 36 per minute, and he was bathed in sweat. Examination of the eyes showed the pupils moderately dilated, reacting to light, left external rectus palsy, and normal fundi. Babinski's sign was positive. Jaw clonus was present, and there was fibrillation of masseters and temporales, but no paresis. There were intermittent clonic movements of the right arm and of both legs, with continuous athetoid movements of hands and feet. The deep reflexes were increased, the abdominal reflexes absent, and the plantar reflexes extensor. There was incontinence of urine. The blood pressure was 140/80 mm. Hg, and the cerebrospinal fluid contained 210 mg. of protein per 100 c.cm.

By July 8 the patient was in deep coma, with pupils contracted and fixed, and all deep reflexes absent. His condition rapidly worsened, and he died.

This case demonstrates the "three stages" preceding the coma which leads to death.

Case 4.—A Pioneer, age and weight unknown, classified as "Others," was admitted on April 4, 1944, to the venereal disease centre, Serampore. The blood Wassermann and Kahn reactions were positive. He received three injections of "Evarsan" at bi-weekly intervals, a total of 0·9 g., and had no reaction.

On April 18 the blood Kahn reaction was still positive. On April 25, thirteen days after the first injection, the patient took a normal meal and then collapsed where he was sitting, after which he was unable to answer questions. He was not unconscious, but stupid (stage two). He received 1 c.cm. of adrenaline intramuscularly at 14.40 hours, the dose being repeated at 15.10 hours when he also had 5 per cent. glucose saline, 20 c.cm., and calcium gluconate, 10 c.cm. intramuscularly, and a lumbar puncture. He improved, and next day was fully conscious but weak; he was given glucose and milk and kept in bed.

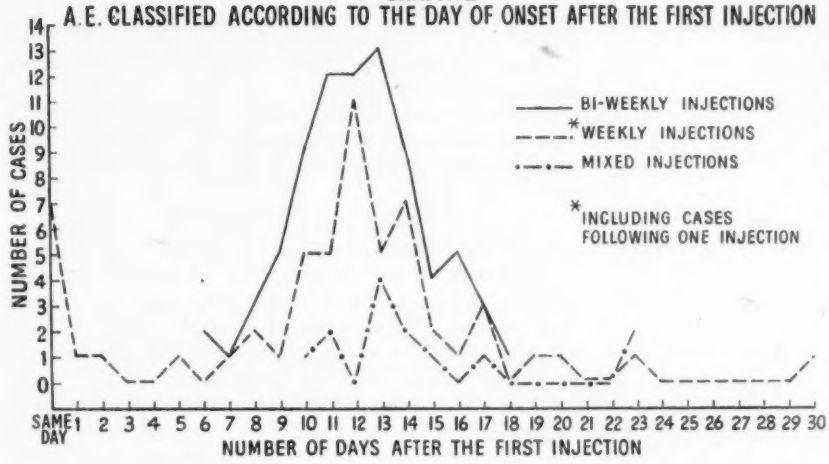
On April 27 he was found collapsed, bathed in sweat, and quite unconscious at approximately 06.15 hours. He was given 1 c.cm. of adrenaline intramuscularly at 06.30 hours, at 08.30 hours, and thereafter at three-hourly intervals; also 50 per cent. glucose, 20 c.cm., intravenously at 07.00 hours, and 100 c.cm. at 15.00

TABLE VI

Diagnosis	No. of cases	Interval between last injection and death in days	Total N.A.B. given in g.	Arsenic contents in mg. %			Arsenic content of brain in % of liver
				Brain	Liver	Kidney	As content
Arsenical encephalopathy ..	6	4	1,35	0·17	0·58	0·66	29·3
Other fatalities during AST ..	3	15	2,95	0·026	0·3	0·43	8·7

Arsenic contents of tissues; average values.

GRAPH 2
A.E. CLASSIFIED ACCORDING TO THE DAY OF ONSET AFTER THE FIRST INJECTION



hours. Fischer's solution, 100 c.cm., was administered at 10.30 hours, and 5 per cent. glucose saline by drip method intravenously, starting at 08.30 hours and continuing up to 18.00 hours—total 200 c.cm.

He died at 09.19 hours on the following day after having developed hyperpyrexia. The cerebrospinal fluid was clear and colourless, with 48 lymphocytes and 12 polymorphs per c.cm., protein 100 mg. per 100 c.cm. The Nonne-Appelt reaction was weakly positive, the Wassermann positive. There was no albumin, but some sugar in the urine. The white blood count was 5,800 per c.mm., polymorphs 65 per cent., lymphocytes 30 per cent., monocytes 4 per cent., eosinophils 1 per cent. Bleeding and clotting times were normal. Red blood cells were 4,800,000 per c.mm., Hb 90 per cent., and there were no malaria parasites.

At necropsy examination twenty-three hours after death the body was seen to be that of a well-nourished young Indian male with healing pubic region sores. There was a faded corymbse secondary rash, post-mortem bruising and discoloration, and slight generalized adenitis. The tongue, pharynx, fauces, and trachea showed considerable post-mortem changes. There were no adhesions in the lungs, but basal congestion with marked crepitus. The pericardium, aorta, and coronary arteries were normal, and also the œsophagus, stomach, and intestines.

Histological examination of the liver showed focal round-cell infiltration with peripheral histiocytic and fibroblastic proliferation and occasional central necrosis; a few histocytic giant cells, and also symplasmic giant cells formed by degenerating liver cells, were seen. Reticulum stain showed overgrowth of delicate reticulum fibres in the areas of necrosis. There was regeneration of liver cells in the neighbourhood under formation of pseudolobules and there were also foci of scar formation. A diagnosis of syphilitic hepatitis with early syphilitic cirrhosis was made.

The medulla oblongata showed occasional perivascular round cells, but no other pathological changes were detected.

In the midbrain there was mild thickening of the meninges, mild proliferation of the astroglia subpial, and perivascular necrosis around some of the large rami perforantes, with demyelination. In the cerebellum there was hyperæmic congestion of the meninges. In the cortex the meninges were moderately thickened, with scanty round-cell infiltration. The meningeal vessels were congested, and there was hyperæmic congestion of the cortex and of the subcortical white matter. There was no evidence of hæmorrhage. The round cells in the meninges were lymphocytes and histiocytes.

This was a case of relapse.

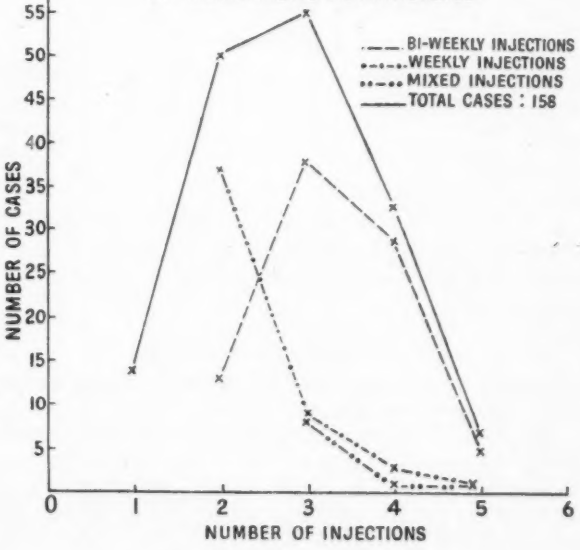
Case 5.—A Sepoy, age and weight unknown, was admitted to the venereal disease centre on Dec. 9, 1943, with a penile sore. The blood Wassermann was strongly positive, the Kahn positive. He had two injections of N.A.B. at a week's interval, total 0·6 g.

On Dec. 26, eleven days after the first injection, he was found to be behaving abnormally. Pupils were normal and reacted to light. There was retention of urine but no rise of temperature. He died eight hours later.

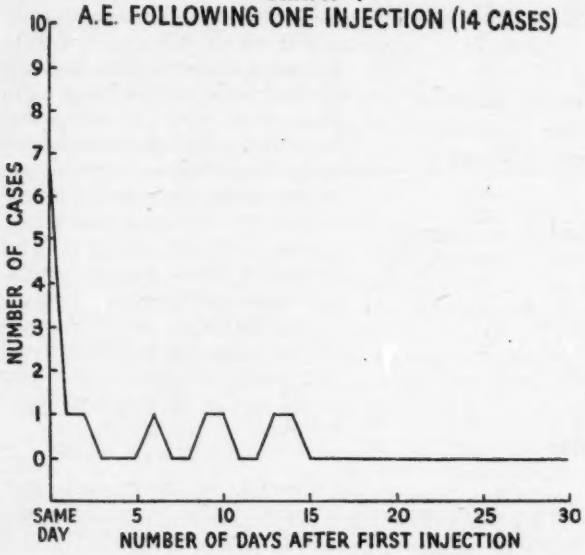
Necropsy showed an Indian male of average build, with bloodstained froth round the mouth. The pleura was free, but there was œdema of the lungs. Heart, abdominal cavity, liver, spleen, bladder, and prostate were normal. The brain showed confluent punctate hæmorrhages and hæmorrhagic softening in the pes of the pons.

Histological examination of the cortex and subcortical

GRAPH 3
A.E. CLASSIFIED ACCORDING TO THE NUMBER OF INJECTIONS ADMINISTERED



GRAPH 4
A.E. FOLLOWING ONE INJECTION (14 CASES)



white matter showed hyperæmic congestion. The subcortical vessels showed severe distention of the perivascular space by homogeneous viscous proteinic material. There were scanty round cells perivascularly. Œdema was present.

The pes pontis showed engorgement of the large vessels and changes of the same type as described in the cortex. There was also extensive confluent capillary hæmorrhage of the ring type, and occasional perivascular hæmorrhage. Extensive necrobiotic changes existed in the neighbouring brain substance with a tendency towards homogenization. There was œdema.

The liver showed hyperæmic congestion, occasional fatty change, and marked periportal round-cell infiltration.

The spleen showed hæmorrhagic patches in the pulp.

This was a case of "hæmorrhagic arsenical encephalopathy."

Pathology

This report is based on nineteen post-mortem examinations with subsequent histological examination. The central nervous system and internal organs of forty-one additional cases were also examined histologically. In view of the fact that the histological lesions are the same as in classical "hæmorrhagic arsenical encephalopathy" and differ only in numbers and intensity, the account will be brief.

Macroscopic Examination

External Appearance.—A healing or healed penile sore was a common feature.

Skull and Brain.—Congestion of the meningeal veins was a constant feature. The most frequent findings were: a mild swelling of the brain, a pale appearance of the white matter; the grey matter was either normal or congested. The brain was not "wet." Only one case showed a pressure cone (of the cerebellum), and only two showed the appearance of "pink brain." Subarachnoid ecchymoses were seen occasionally.

Chest.—There was usually hypostatic congestion of the lungs.

Other Organs.—The spleen was commonly enlarged; malarial pigmentation was found only in one case, while smears yielded negative results for malarial parasites.

Histological Examination

(The number of cases examined is given in parentheses).

Liver (45).—Fatty changes were a common feature; small hæmorrhages, focal fatty degeneration, and foci of liver cell necrobiosis were seen occasionally. Specific gummatous lesions were seen in three cases only (Fig. 1). Periportal infiltration with lymphocytes, plasma cells, and occasional eosinophils was a prominent and nearly constant feature.

Spleen (30).—Cases with splenic enlargement showed congestion, hæmorrhage, and a moderate degree of pulp hyperplasia.

Suprarenals (20).—Fatty infiltration of the cortex was commonly found.

Kidneys (26).—The commonest findings were hyperæmia, congestion, and cloudy swelling.

Central Nervous System (60).—The entire nervous system was examined systematically.

There was only a small number of histological lesions, and they were usually of low-grade intensity. The brain stem and white matter were as a rule more involved than the cortex and the medulla oblongata. Congestion and stasis were a constant feature—predominantly involving the veins and the arterioles. Hæmorrhages were scanty and usually only perivascular. Capillary hæmorrhage of the "ring" type was found only rarely (Fig. 2). There was normally no direct evidence of endothelial damage (Fig. 3). Thrombotic changes were rare (Fig. 4). A viscous exudation of plasma, perivenous and periarterial (but not around capillaries) was a fairly constant finding (Fig. 5).

Inflammatory changes in the form of perivascular round-cell infiltration were seen in nearly all cases (Fig. 6). Patchy round-cell infiltration of the meninges was also seen (Figs. 7 and 8). Unlike the vascular changes, the round-cell infiltration was also commonly found in the cortex. All the inflammatory changes were mild. The inflammatory cells were lymphocytes, histiocytes, and plasma cells.

Parenchymatous changes were also mild (Fig. 9), and were partly secondary to perivascular hæmorrhage and viscous exudation. Nerve-cell changes were absent.

Though all the different types of lesions followed the same pattern of distribution, a considerable independence of individual lesions was observed; perivascular and round-cell infiltration were seen without hæmorrhage, and viscous exudation independent of hæmorrhage.

There was mild interstitial œdema. (Gross œdema with its macroscopical signs was absent.)

Some cases showed atypical features. Two showed hæmorrhagic features—one of them in the form of purpuric capillary hæmorrhages of the "ring" type in the subcortical white matter, and the other in the form

of a confluent capillary and perivascular hæmorrhage in the pons. Two cases showed definite perivascular demyelinating lesions not secondary to viscous exudation or hæmorrhage. The lesions were situated in the occipital white matter in one case, and in the midbrain in the other (Fig. 10).

ARSENIC CONTENTS OF TISSUES.—These were determined on tissue digests with the Gutzeit method. Table VI shows the average values obtained. Our values are in good agreement with those recorded by Osterberg and Kernohan (1934).

Comparison of Arsenical Encephalopathy in Indian Troops with Classical Hæmorrhagic Encephalopathy

Comparison of " arsenical encephalopathy in Indian troops," as described here, with typical " hæmorrhagic encephalopathy," as recorded in the literature, shows a seemingly adequate pathological basis in the latter group, and macroscopical and histological findings insufficient to explain the severity of the clinical picture in the former. The pathological relationship between the two conditions is stressed by the occasional occurrence of typical hæmorrhagic cases in this series, and by two cases with typical demyelinating lesions. It is noteworthy that fully developed demyelinating lesions were seen by Dorothy Russell only in cases of four and six days' duration. One of our cases presenting fully developed demyelination is a case of " relapse " of 71 hours' duration from the onset to the fatal outcome ; the second case was of 36 hours' duration only. (The interpretation of this is somewhat confused, as the patient had been vaccinated four days before the onset of arsenical encephalopathy ; his reaction to vaccination was " modified positive.") The possibility that demyelinating lesions observed in cases of considerable duration—4 to 6 days in the series of Dorothy Russell, 71 hours and 36 hours in this series—are the histological manifestation of functional alterations at corresponding sites, that is, the perivenous and periarterial white matter, in cases of shorter duration, has been considered. Occasional perivascular swelling of myelin sheaths and axis cylinders, independent from hæmorrhage, as well as an occasional minute focus of early perivascular necrosis, is recorded by Dorothy Russell (1937) in one case of classical hæmorrhagic arsenical encephalopathy of six hours' duration.

Arsenical encephalopathy in Indian troops is the " pathological equivalent " of classical " hæmorrhagic encephalopathy."

Non-hæmorrhagic cases of arsenical encephalopathy are recorded occasionally in the literature. It seems that the number of typical hæmorrhagic cases under record is somewhat exaggerated, as there is a tendency to regard cases with a few perivascular hæmorrhages as examples of it. In Halcrow's (1943) case " the lesions (hæmorrhages and others) present were not numerous, therefore careful searching was necessary. Some blocks of brain tissue revealed no lesions."

Visible damage to the capillary endothelium with subsequent thrombosis and rhexis of blood vessels is far more prominent in hæmorrhagic arsenical encephalopathy than in arsenical encephalopathy observed in Indian troops. Viscous perivascular exudation was seen perivenously and periarterially. It indicates loss of selective permeability of blood-vessels. It is of interest that viscous perivascular exudation was seen in the absence of gross œdema. In cases of arsenical encephalopathy with insufficient pathological findings recorded in the literature, gross œdema was regarded as the cause of the clinical picture and fatal outcome. The examination of this series shows that gross œdema sufficient to produce increased intracranial pressure is not a feature of the condition.

The macroscopical and histological findings of arsenical encephalopathy in Indian troops are interpreted here rather as signs than as the cause of the clinical picture.

The presence of a circulatory disturbance is indicated by stasis, congestion, and perivascular and capillary hæmorrhage ; viscous perivascular exudation indicating the loss of selective permeability of blood vessels.

Comparison of the pathological findings and of the clinical picture in this series with the findings in classical " hæmorrhagic encephalopathy " raises some doubt that hæmorrhage itself is the only cause of the clinical picture in hæmorrhagic encephalopathy, as the clinical picture may develop in the absence of gross or purpuric hæmorrhage.

Inflammatory changes are more constant in this series than in classical hæmorrhagic encephalopathy, but the inflammatory changes are only mild. Koenigstein and Spiegel (1920) have referred to the difficulty of distinguishing between inflammatory lesions due to syphilis and inflammatory lesions due to arsenical encephalopathy in hæmorrhagic cases. The evidence of mild thickening of blood vessels with obvious perivascular round-cell infiltration, the coexistence of patchy meningeal round-cell infiltration, and the predominantly histiocytic character of the inflammatory cells, suggest in our opinion that at least part of the inflammatory lesions is the manifestation of preclinical neurosyphilis. In good agreement with this interpretation of the inflammatory lesions is the evidence in the literature that " a large proportion of the cases of syphilis show abnormalities in the fluid early in the disease " (Merritt and Fremont-Smith, 1938). It is pointed

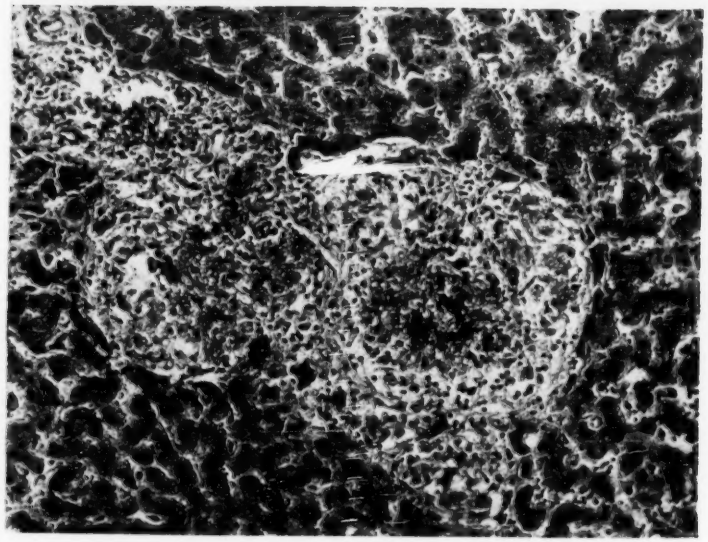


FIG. 1.—Liver ; small gummatous periportal lesions.

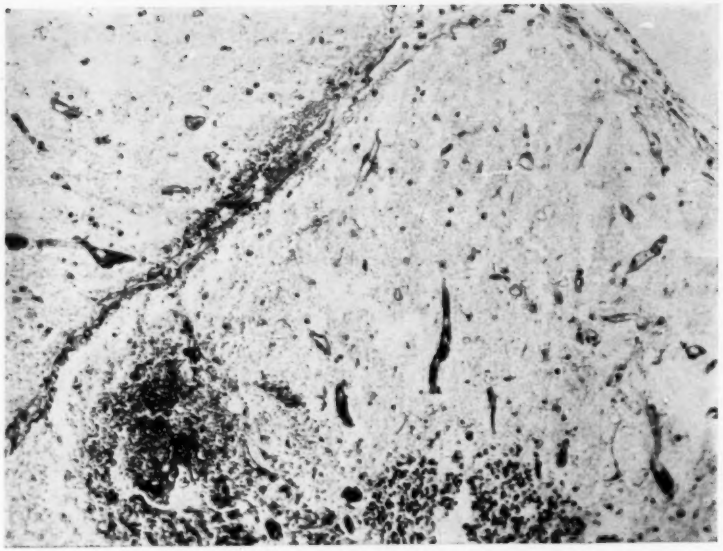


FIG. 3.—Cerebellum : meningeal ecchymosis, capillary vasodilatation with swelling of endothelial cells, and capillary hæmorrhages.

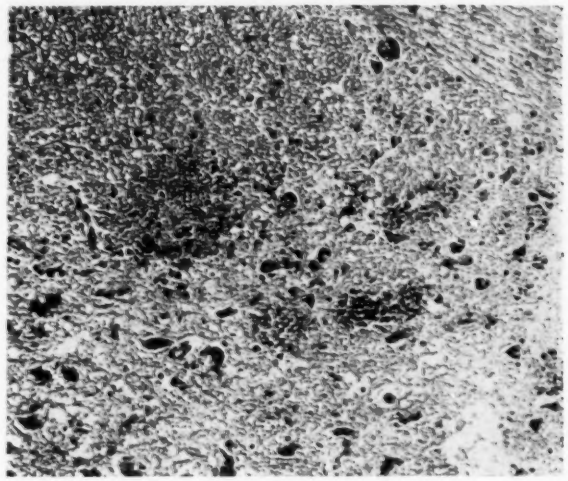


FIG. 2.—Pons ; capillary hæmorrhages of the ring type.

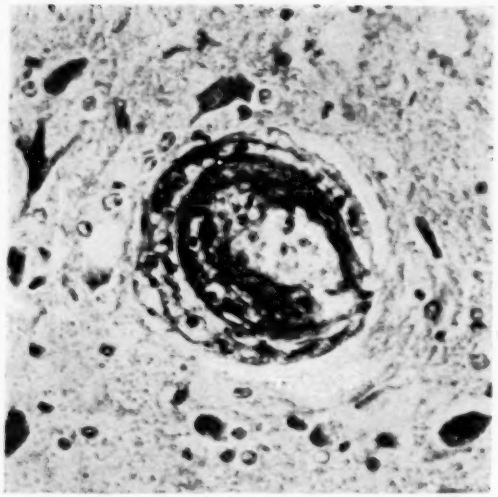


FIG. 4.—Pons ; incomplete thrombosis of a venule.

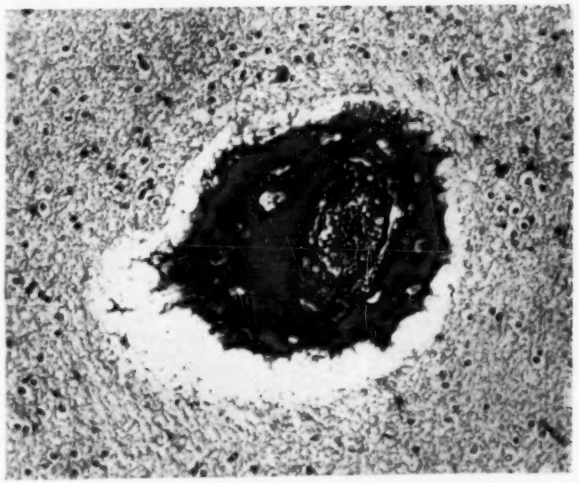


FIG. 5.—Subcortical white matter from the same case as in Fig. 4 ; perivascular viscous exudation.

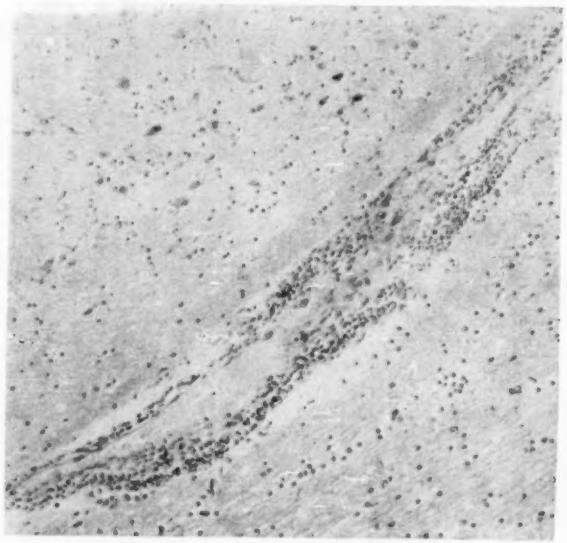


FIG. 6.—Pons ; perivascular round-cell infiltration.

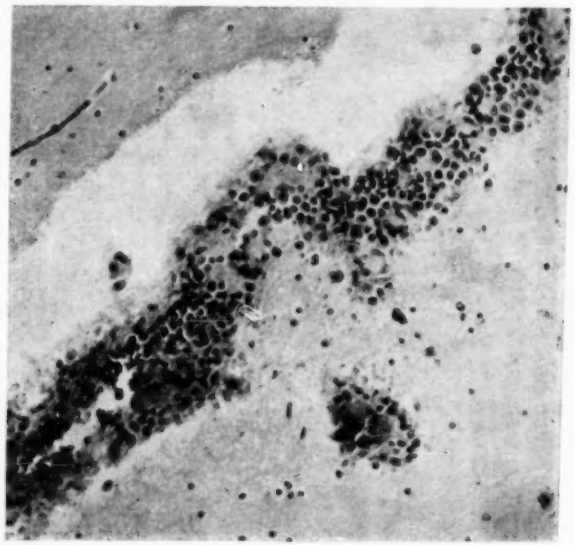


FIG. 7.—Cortex ; meningeal round-cell infiltration.

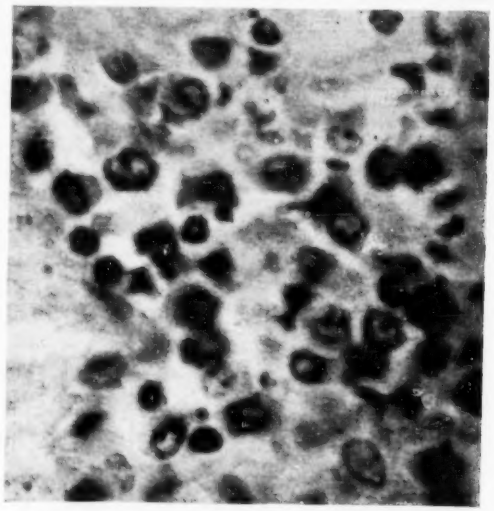


FIG. 8.—Enlargement of Fig. 7 ; lymphocytes and histiocytes.

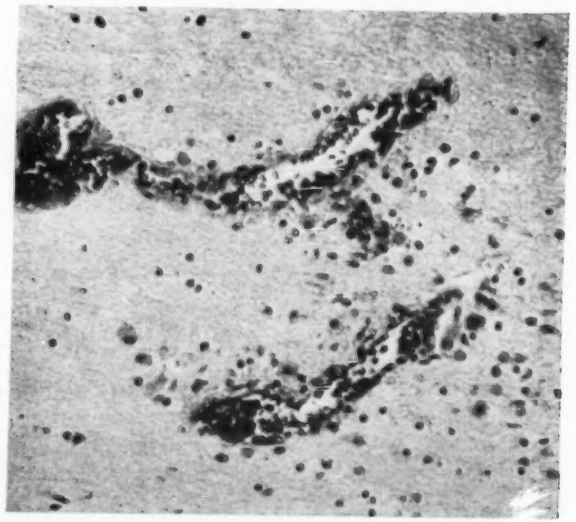


FIG. 9.—Subcortical white matter ; perivascular neuroglioproliferation ; presence of mobile cells.

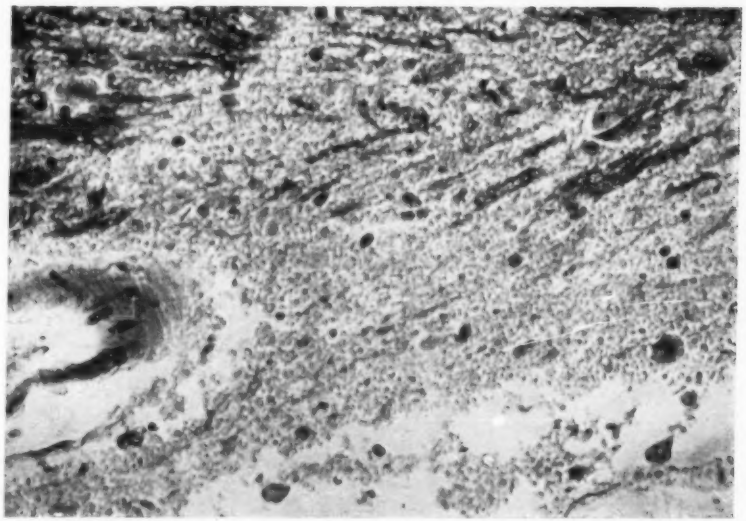


FIG. 10.—Midbrain ; perivascular necrosis and demyelination.

out that none of our cases shows gross evidence of meningo-vascular syphilis.

Specific lesions in the internal organs other than the central nervous system were confined to the liver. Three cases show gumma formation, and one case syphilitic hepatitis. Marked periportal round-cell infiltration was interpreted as a manifestation of syphilis.

Ætiology

It seems that the facts known and some additional facts emerging from this investigation are insufficient to form the basis of a satisfactory and comprehensive explanation as to the ætiology of arsenical encephalopathy. For this reason only a short discussion of the various theories in being, and interpolation of the findings recorded in this investigation, is attempted here, the guiding principle of the discussion being to separate so far as possible the *cause* of the condition from its *mechanism*.

Cause

Activation of a pre-existing virus has been considered as the cause of arsenical encephalopathy. In other words, arsenical encephalitis would be a virus disease, the virus being pre-existent in the body of the individual and activated by the administration of a trivalent organic arsenical compound. This hypothesis bases its claims on the similarity of the picture of acute perivascular myelinoclasis and hæmorrhagic encephalitis following various virus infections or antirabic treatment, with the picture of hæmorrhagic and demyelinating arsenical encephalopathy. It is admitted that the exact relationship between the original virus infections and the subsequent encephalitis in the group of diseases referred to is not known. No additional facts have been found here to give more weight to the infection theory, so far as activation of a pre-existing virus is concerned.

Sterilization of syringes after each injection had no influence on the incidence rate of arsenical encephalopathy, and when two cases of arsenical encephalopathy occurred on the same day a subsequent check on the order in which the patients were injected revealed that the patients belonged to different batches. There seems to be no proof that a virus is carried by the syringe.

Various authors have pointed to the complex of Jarisch Herxheimer's reaction as the cause of arsenical encephalopathy. Our material gives no evidence in this direction. If the condition is Jarisch Herxheimer's reaction it should follow twenty-four hours after the first injection of the N.A.B., and if this be dispensed with one would expect that the cerebrospinal fluid would be Wassermann-positive in these cases at the time of the arsenical encephalopathy. Out of twenty-five cases examined, the cerebrospinal fluid Wassermann was negative in 17 and positive in 8. For that reason it is thought that Jarisch Herxheimer's reaction is not the cause of arsenical encephalopathy in this series.

Authors who believe that acute perivascular myelinoclasis following various infections is the effect of sensitization, and not a virus disease in itself, expressed the opinion that arsenical encephalopathy is the result of sensitization against arsenic. Various points are in favour of this assumption, as the time of onset of arsenical encephalopathy after the first injection is the same as the common time of onset of acute perivascular myelinoclasis or hæmorrhagic encephalitis after the original virus infection ; also the interval between the onset of serum sickness and administration of serum is of comparable order. Trivalent organic arsenical compounds, especially if administered together with serum, produced sensitization and anaphylactic reaction in guinea-pigs (Landsteiner and Jacobs, 1936). For that reason sensitization cannot be excluded beyond doubt as a causative factor of arsenical encephalopathy. Reports of untoward accidents following administration of arsenic compounds in patients who survived an attack of arsenical encephalopathy are recorded in the literature. An observation to the contrary was put at our disposal by Captain L. Cohen, R.A.M.C. After having had an attack of arsenical encephalopathy a patient received erroneously an injection of N.A.B., with no ill effects. A second case treated with intramuscular injections of a trivalent arsenical compound subsequent to an attack of arsenical encephalopathy showed also no untoward effects.

Finally, toxic effects of trivalent organic arsenical compounds have also been regarded as the cause of arsenical encephalopathy. Osterberg and Kernohan (1934) reported " relatively high arsenic contents," especially of the white matter of the cerebrum, in cases of hæmorrhagic arsenical encephalopathy. " It has been suggested by Voegtlin and his co-workers that the same mechanism by which the arsenicals are lethal to parasites (spirochætes) is apparently concerned in their toxicity for the tissues of the host " (quoted from Goodman and Gilman, 1941).

After one injection of arsphenamine 50 to 70 per cent. of the arsenic is excreted within one week, and this is a determinant of the weekly interval between injections in patients (Goodman and Gilman, 1941). The standard treatment of syphilis introduced on this basis—weekly injections of trivalent organic arsenicals—gives a high percentage of cures with a minimum of untoward effects and fatalities.

In the endeavour to shorten the time of treatment and to ensure a higher percentage of cures of syphilis, massive and continuous treatment with N.A.B. and mapharside was introduced. Increased spirocidal toxicity obtained by these means was accompanied by increased tissue toxicity.

The Army treatment of syphilis with bi-weekly injections is a compromise between massive treatment and standard treatment with weekly injections. In this investigation it was found that the incidence rate of arsenical encephalopathy in certain groups of Indians—Madrassis and Mahrattas—was significantly higher with bi-weekly than with weekly injections ; this fact is relevant to any hypothesis of causation.

It is often recorded in the literature that arsenical encephalopathy is as common with high as with low doses of N.A.B. Our material does not allow any statement to be made to this effect, as the dosage was standardized according to body weight and for that reason comparable in the different dosage groups.

The following line of thought has been taken here. The basis of the weekly standard treatment was the knowledge that a high percentage of arsenic (50 to 70 per cent.) is excreted within one week after injection. Treatment with weekly injections avoids accumulation of arsenic. It appears logical that if treatment is given at bi-weekly intervals, with either the same dose or even with a somewhat lower dose of N.A.B., a higher level of arsenic will be maintained for a longer time. As bi-weekly treatment is apparently associated with an increased incidence rate of arsenical encephalopathy, it is concluded that the maintenance of a high level of N.A.B. increases the incidence rate of arsenical encephalopathy. Such an effect of a relatively high arsenic concentration maintained in the body for a comparatively long time indicates a causative relationship between the incidence rate of arsenical encephalopathy and the frequency of injections of N.A.B.

Mechanism

It is generally agreed that the mechanism involved in hæmorrhagic encephalopathy is vascular damage ; " capillary encephalorrhagy " is the term proposed by Globus and Ginsberg (1933). Also thrombosis has been regarded as the cause of hæmorrhagic and necrotic lesions ; damage to the endothelium of blood vessels with swelling and fatty degeneration is recorded. The mechanism of perivenous and peri-arterial demyelination is not understood. A toxin has been held responsible by Dorothy Russell. In rare non-hæmorrhagic cases œdema and vasoparalysis (Scheinker, 1944) have been regarded since Ehrlich (1914) as the cause of the clinical picture and fatal outcome.

An attempt to analyse the lesions observed in this series as part of the mechanism producing arsenical encephalopathy shows the following : the presence of vascular and circulatory disturbances is indicated by stasis, congestion, hæmorrhage, and occasional thrombosis ; capillary hæmorrhages, usually indicating a severe vascular and circulatory disturbance, are scarce.

An important feature of the condition is the presence of perivascular viscous exudation of plasma indicating loss of selective permeability of blood vessels. This is also indicated by the high protein values of the cerebrospinal fluid observed in arsenical encephalopathy, and their importance is stressed by the observation that the average protein content of the cerebrospinal fluid has been significantly lower in cases which recovered than in cases with fatal outcome. It is stressed that this loss of selective permeability recorded here is not associated with gross œdema, the discrepancy between the amount of perivascular viscous exudation and the absence of the effects of severe œdema is obvious. Not only is the intracranial pressure, determined by lumbar puncture, within normal limits, but also the fundus is devoid of papillœdema, and the anatomical manifestations of increased intracranial pressure, that is, pressure cones and flattened gyri, are also absent. It seems of interest that the intracranial pressure was often below average, the blood pressure being normal.

The following working hypothesis may be attempted, although no special claims can be laid on it. Administration of N.A.B. produces damage to cerebral blood vessels, resulting in loss of selective permeability. Subsequently N.A.B. and split products of N.A.B. penetrate into the nervous tissue, mainly perivenously and periarterially, and interfere there with oxydation systems of the parenchyma. In hæmorrhagic cases the vascular damage is more prominent in the form of hæmorrhage and œdema ; in non-hæmorrhagic cases the invisible tissue toxic effect is more prominent and may manifest itself at later stages of the disease as perivascular necrosis and demyelination.

Summary

1. Arsenical encephalopathy in Indian troops is the pathological equivalent of classical hæmorrhagic arsenical encephalopathy ; it has the same time of onset and the same clinical picture as the classical condition, but it differs by a comparatively high incidence rate and by the absence of gross hæmorrhagic or purpuric lesions. The relationship to the classical condition is stressed by occasional typical hæmorrhagic cases and by cases showing demyelination.

2. The " racial " incidence of arsenical encephalopathy is high in Indians ; it is considered that part of it is " social " incidence.

3. An attack of malaria during or shortly before antisyphilitic treatment is an important factor in increasing the incidence of arsenical encephalopathy.

4. The incidence rate of arsenical encephalopathy in Indian troops treated with weekly injections of N.A.B. is of the same order as the incidence rate in Indian civilians.

5. The increase in the incidence rate of arsenical encephalopathy in Indian troops, as compared with Indian civilians and observed since 1943, is the effect of the treatment of syphilis with bi-weekly injections of N.A.B.

6. The increased incidence rate of arsenical encephalopathy following bi-weekly injections of N.A.B. is not proportionate in all provincial groups of Indian troops. The incidence rate is significantly higher in Madrassis and Mahrattas, and only moderately increased in Indians from other provinces.

7. The incidence rate of arsenical encephalopathy in sero-positive primary and secondary syphilis is not higher than in sero-negative primary syphilis. The higher incidence rate of arsenical encephalopathy in sero-negative primary syphilis as compared with the two other groups is still below statistical significance in this series.

8. Four successive stages of the clinical picture can be separated. The first three stages are reversible, all cases reaching the fourth stage—coma—are fatal.

9. The protein content of the cerebrospinal fluid in arsenical encephalopathy is usually greatly increased without proportionate increase of the cell count ; the average protein content in cases which recover is significantly below the average in fatal cases. The high protein content of the cerebrospinal fluid is interpreted as the manifestation of loss of selective permeability of blood vessels.

10. The arsenic content of the brain in this series was relatively high, and of the same order as reported by Osterberg and Kernohan (1934) in cases of classical hæmorrhagic arsenical encephalopathy.

11. The tissue pathological findings are signs rather than the cause of the condition. They indicate vascular damage, circulatory disturbance, and loss of selective permeability of blood vessels.

12. Gross œdema, increasing the intracranial pressure, is not a feature of the condition. This is substantiated by the absence of paillœdema, the average pressure of the cerebrospinal fluid at lumbar puncture, and the absence of pressure cones.

13. The fact that a relatively high level of N.A.B. is maintained for a comparatively long time if treatment is given at bi-weekly intervals, together with the subsequently increased incidence rate of arsenical encephalopathy, indicates a causative relationship between the level of arsenic maintained in the tissues, the frequency of injections of N.A.B., and the incidence rate of arsenical encephalopathy.

14. Arsenical encephalopathy subsequent to a standardized form of antisyphilitic treatment is considered here as a tissue toxic effect of trivalent organic arsenical compounds in persons predisposed racially, socially (nutrition), and individually (e.g., malaria). Whereas vascular damage is more prominent in cases of classical hæmorrhagic encephalopathy, functional and eventual anatomical damage to the parenchyma was more conspicuous in arsenical encephalopathy in Indian troops.

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APHASIA STUDIED IN PATIENTS WITH MISSILE WOUNDS

BY

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THE objects of this investigation were to find out how far aphasic manifestations can be classified into useful groups, whether such classification corresponds with topographical arrangements in the cerebral cortex, and whether the approach to aphasia can be simplified by adequate terminology.

Material, Tests, and Records

Forty-six convalescent cases of penetrating missile wounds of the dominant hemisphere, having some relevant symptoms, were selected at the Military Hospital for Head Injuries, Oxford, and subjected to various tests. Two were left-handed, with wounds of the right hemisphere, and two others had multiple brain injuries. One was practically illiterate, probably owing to a congenital defect which left his general intelligence fairly intact.

Each patient was given a short explanation and then his response to questions about his speech trouble was taken down verbatim. This was followed by the spontaneous naming by free association of a maximum number of animals in one minute, and a vocabulary test. These tests allowed estimation of the disturbance of articulation, inflection, and speed, of the tendency to paraphasia, jargon, and syntactical errors, and of the difficulty in finding words for ideas. The patient's responses to the first sixteen words of the Standford-Binet vocabulary test were recorded verbatim, and found to be useful as a direct, if somewhat formal means of estimating his expressive power. Eight words were given orally, then the patient was asked to read and explain the remaining eight. Next, ten coloured pictures of simple objects were exposed to be named. The patient was then asked to point to that pictured object which was named by the examiner, and finally to the one the name of which was printed on a slip. This was an easy test for naming, and for the understanding of written and spoken words.

Understanding was further tested by the patient's ability to execute simple commands with regard to his body, the most difficult involving three different actions to be done synchronously. Reading monosyllables (three-letter words) with a time limit of one minute was another check on speed and ability to convert visual symbols into those of sound. Reading of seven figures from one to four digits, and eventually a twenty-word sentence including three or four rather difficult words, completed the evaluation of this aspect of speech.

The writing tests were graduated from a dictation of ten words, consisting of one to ten letters, to the figures and the sentence previously read. From this the ability to spell was computed. If the patient failed in this test he was asked to copy ten single letters, seven figures, and the twenty-word sentence. If the disturbance was not gross, the simplest tests were sometimes omitted. In the end the patients were asked to copy the Stanford-Binet shapes from the mental age tests (form M) for nine and twelve years, and to perform the first five patterns of the Kohs' blocks test, in order to estimate visual and constructive ability. Finally they were given the serial seven test, and usually an abbreviated (halved) form of Raven's Matrices to test calculation and abstract thinking.

At some stage of the session a neurological examination was made.

The following (Case 1) is an example of the verbatim responses to direct questions and the vocabulary test. The patient, a trooper aged 22, had been a storekeeper and before his injury was fairly talkative. He was right-handed. Six months before his examination he had suffered severe concussion.

(What is the matter with your speech?) . . . Hm. To say names. (Is it that you can't remember them?) No—really. Hm. Sometimes yes; but I have no idea how the noise—no . . . (Do you mean the sound?) Yes, sound is foun—is formed. (Can you understand what is being said to you?) Oh yes. (How about reading?) Out loud? (Can you read to yourself?) Yes. (Are you slow, when you are reading to yourself?) (Slower than you used to be?) Yes, but not so much. (How is your writing?) Writing I have to think of every word. I—it—takes—me—about one hour to do—a—write—a—pace—page—page.

BINET VOCABULARY ORAL

Word	*Answer*
Orange:	Something to eat.
Envelope:	To h-hold—something—in—to say the letter.
Straw:	Soming which—in—the Army—is—used—to—make—a—bed.

Puddle :	Water. (Where ?) In the gra—no—on the—ground.
Tap :	Cap—t—tap—a for-leg—a for-tis—em—to turn—— (What ?) Water.
Gown :	Gown—a piece of cloth—usually made—made—em—u—use—used by women sometimes.
Eyelash :	Eye—lash—em—(points to his own) To keep—something—dust and things, like that—out—of the—eye.
Roar :	War—roar—a tank roars—a tank wars, yes.

READ FROM PRINT

Scorch :	Scour — scorch, scorch — to — burn — nearly burn—something—to nearly, nearly burn something.
Muzzle :	Muzzle — mustle — mm — mustle—sometimes, when dogs go—sometimes—when dogs—are—too—fierce—they—are—put—on—a—muzzle.
Haste :	Haste—he—was—in a—haste—no—yes.
Lecture :	Lecshure — lecture — the — lecture — supposing — you — tell — I'm — me—no—supposing that—I was—to done do something wrong you would—lecture me.
Mars :	Mars—Mars ?—Mars—a—planet.
Skill :	Still—skill—still—skill—skill—he had he had a neck—neck—no—he was—very clever.
Juggler :	Juggler—jug—juggler—you can see jugglers—at—any fair.
Peculiarity :	Per—per—I can't—even—see it—em—em—the—thee—the.

The number of errors, or time needed in the various tests, was as follows :

1. Spontaneous word production (animals) : cat, god, goldfic-, goldfish, hem, toad, snake, pig, sheep, cow, bull, mmm— ..	9 in 1 minute
2. Binet vocabulary : 1–8 orally ..	8 correct
9–16 reading..	7 correct
3. Naming 10 pictures or objects ..	all correct
4. Showing 10 objects when names are given	all correct
Showing 10 objects when names are given in print	all correct
5. Reading monosyllables in 1 minute	34 out of 40 correct
6. Reading 7 figures : 6, ah 5, 8, 3, 29, 4–7, 615, 8372	all 7 correct
7. Reading 1 sentence (20 words) : " look–if you look back on your own–in–ed–u–ed–cru–ed–ce–edcru–ed–edculation "	
8. Dictation : 10 words	4 mistakes
sentence (20 words)	not attempted
7 figures (516 after many trials) ..	all correct
9. Copying : 10 letters	not done
20 word sentence	no mistakes
7 figures	not done
3 simple shapes	no mistakes
10. Kohs' blocks : I	6 seconds
II	12 seconds
III	30 seconds
IV	15 seconds
V	15 seconds
11. 100–7 test : 93, 86, 79, 72, 65, 58, 51, 44, 35, no 37, 30, 23, 16, 9, 2 ...	3 minutes, no mistakes
12. Raven's matrices (abbreviated) ..	not done

Fig. 1 shows this patient's " aphasia chart," which is an attempt at a graphic display of the disabilities. These charts are not mathematically accurate, which cannot be expected in work of this kind. However, in the study of aphasia it is imperative to assess the relative preponderance of one feature of the disorder over another, and this method of grading was, therefore, found helpful. In the absence of any one aspect of the disturbance the mark " O " was given ; if doubtful it was charted under " 1," if slight under " 2 " ; moderate " 3," marked " 4," and if extreme " 5." Both physical and mental features were included, and were so arranged that what commonly are called " motor " disturbances of speech were grouped with neurological motor disorders, and signs of " sensory " aphasia with defects of visual fields, posture sense, etc.

Each brain lesion was charted after careful consideration of the bone defect under the scalp, the skiagrams, the motor, sensory, and perimetric evidence of cortical damage, and the surgeon's report. In the absence of autopsies all these data could give but an approximate estimation of the site and extent of the cortical lesions. In view of the variability both in the size of skulls and brains, and in their mutual relationships, accurate measurements of distances from the edges of the bone defect to certain standard points on the skull were no help. The surface marking thus recorded often included damage in the depth of the hemisphere, where fibres had been destroyed, though their origin in the cortex may have escaped injury. Thus, tracks leading from the wound of entry and also buried foreign bodies were mapped on the chart.

In the " cumulative charts " (Figs. 2 to 11) the outlines of the brain wounds were superimposed. Each diagram assembles all those patients in whom one feature of speech was disordered to at least a moderate degree. These charts give an idea of the relative frequency with which an abnormal clinical characteristic was associated with a certain cortical area. Fig. 12 summarizes the results. In it the cases are arranged in topographical order and plotted against the graduated assessment of their disabilities.

Findings

Disturbances of Articulation, Inflection, and Speed.—The disturbances were marked in 20 out of 41 cases. In all but 2 these disorders occurred together.

One of the exceptions (Case 5) had very little speech disturbance, and his diminished speed was probably due to difficulty in word finding ; the other (Case 32) spoke at a normal speed despite a definite disturbance of articulation and inflection. All 20 had some difficulty in word finding. Neurologically all but the one with very slight aphasia (Case 5) had some definite motor loss in the limbs ; in 12 there was complete or almost complete uselessness of the dominant hand ; 14 had marked loss

APHASIA CHART

No.: 6405115; *Rank:* Trooper; *Age:* 22; *Previous occupation:* storekeeper; *Previous personality:* fairly talkative; *Handedness:* right; *Days after wounding:* 6 months.

Surgeon's Notes: Severe concussion. Initial jargon. Cerebral protrusion. Cavity 11 cm. in length, 3 cm. wide, 3 to 4 cm. deep, involving lateral ventricle.

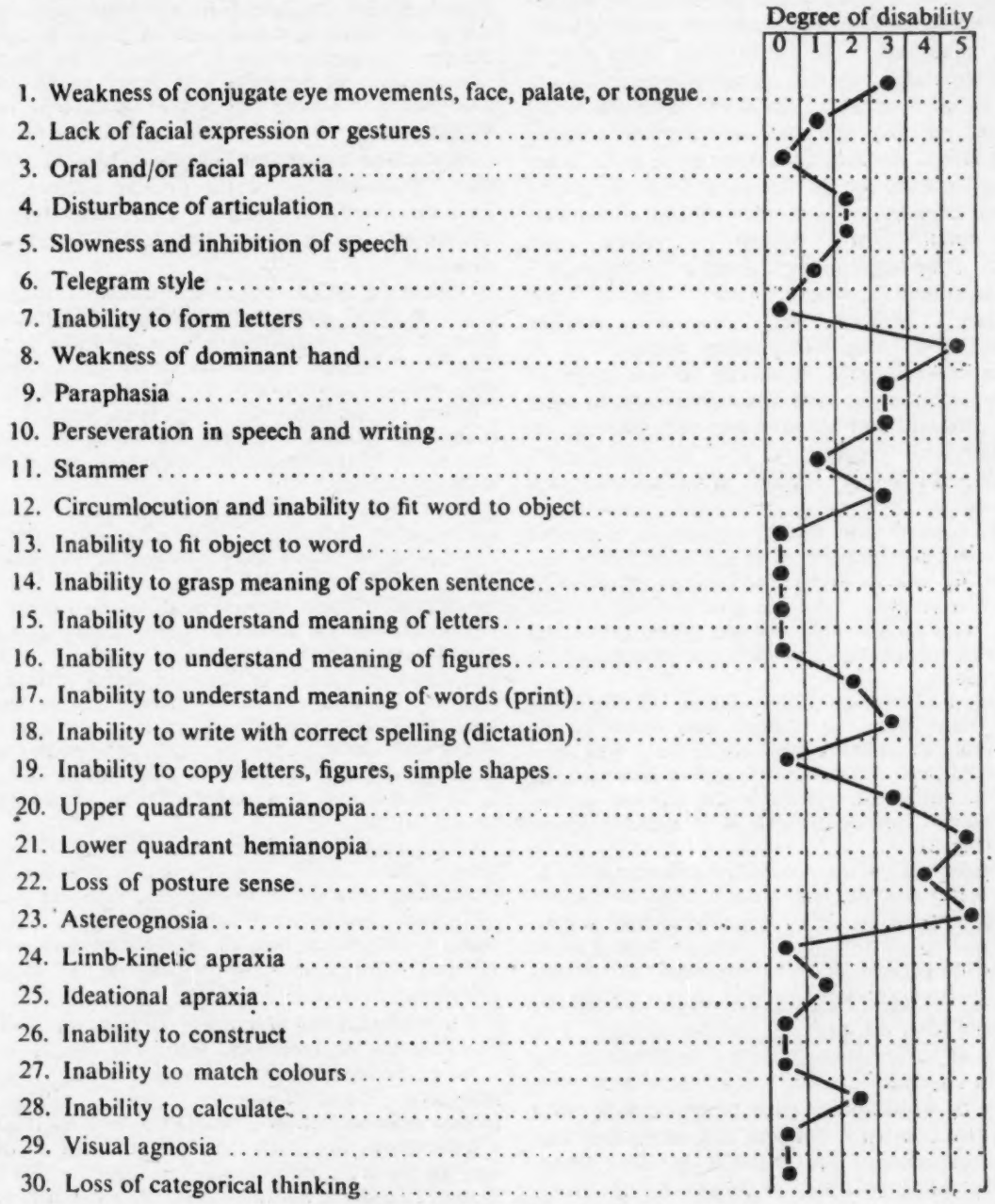

Degree of disability
0 1 2 3 4 5
1. Weakness of conjugate eye movements, face, palate, or tongue
2. Lack of facial expression or gestures
3. Oral and/or facial apraxia
4. Disturbance of articulation
5. Slowness and inhibition of speech
6. Telegram style
7. Inability to form letters
8. Weakness of dominant hand
9. Paraphasia
10. Perseveration in speech and writing
11. Stammer
12. Circumlocution and inability to fit word to object
13. Inability to fit object to word
14. Inability to grasp meaning of spoken sentence
15. Inability to understand meaning of letters
16. Inability to understand meaning of figures
17. Inability to understand meaning of words (print)
18. Inability to write with correct spelling (dictation)
19. Inability to copy letters, figures, simple shapes
20. Upper quadrant hemianopia
21. Lower quadrant hemianopia
22. Loss of posture sense
23. Astereognosia
24. Limb-kinetic apraxia
25. Ideational apraxia
26. Inability to construct
27. Inability to match colours
28. Inability to calculate
29. Visual agnosia
30. Loss of categorical thinking

FIG. 1.

of postural sense with or without astereognosis; in 7 there was marked impairment of the right homonymous visual fields. Twelve had difficulty in using their lips and tongue for blowing, licking, and whistling ("oral apraxia"). This last phenomenon was seen only in patients with predominant disorders of inflection, articulation, and speed (Fig. 2).

Paraphasia.—In contrast to dysarthria the incorrectness of the paraphasic utterance is characterized not so much by indistinctness of pronunciation as by severe distortions of the phonetic pattern, by wholesale substitution of some sounds or sound-complexes, and by omissions. The result often bears only a faint resemblance to the intended word. There seems to be a scale in the severity of the word distortion, possibly indicating different physiological nervous levels. At one end is dysarthria, at the other complete substitution of the correct by an utterly incorrect expression (jargon). Slight distortions were "cotch" for "Scorch," "pa-aste" for "haste," "n-j-ogger" for "juggler," "occasial" for "occasional"; severe ones "toaster" for "postman," "gillery" for "juggler," "predger streamer" for "ship" ("pleasure steamer"). A frequent characteristic, especially in the stage of recovery, was the patient's dissatisfaction with what he was uttering, and his attempts at improving on it ("gillery, no, juggery, no . . ."); involuntary perseveration may play its part, as well as voluntary effort.

The 11 patients with definite paraphasia had some degree of defective auditory comprehension. There was also difficulty in word-finding, and a severe disorder of spelling (paragraphia). All but one had well marked "alexia"; they not only misread words (paralexia) owing to paraphasic slips, but their understanding of the text was poor.

Six (group A) had loss of articulation, inflection, and speed. These were the patients who neurologically showed pronounced motor and sensory loss; 4 of these had marked field defects and 3 marked oral apraxia. The 6 patients already quoted in the previous section had extensive rolando-parietal or rolando-temporal wounds (Fig. 3).

Conversely, none of the remaining 5 patients (group B) had any motor loss, and only 2 had a moderate disturbance of postural sense. Four had marked field defects. None had oral apraxia. The sites of their injuries were temporo-parietal. Fig. 3 shows these two groups.

Jargon.—In this disorder the words uttered by the patient have no meaning for the listener. This is the most severe type of word distortion, being allied to paraphasia but also associated with difficulty in word-finding and understanding, with inability to construct grammatical sentences, and with perseveration. Head (1926, p. 305) rather artificially relegated cases of jargon to his group of "syntactical" aphasia.

One patient (Case 40) defined "lecture": "Neck-exo—ext—exer—but ex—ex— well I can't say it is a nexer by a certain person to a so—odd—wot." And the word "peculiarity": "Ee picoahty—to a luddy." "Envelope": "I know it ees baw I do I know it is do tickle, uful. Too diffilt." This kind of disorder was found in 5 of those cases included in the previous group of paraphasic manifestations. In no case of jargon was there any logorrhœa, that uninhibited flow of unintelligible words which usually accompanies jargon. Variations in temperament may influence the extent of logorrhœa, but its absence in our cases was striking. Guttmann (1942) noted absence of jargon in aphasic children. Jargon notoriously occurs with temporal-lobe lesions; all our cases with jargon had temporal-lobe lesions, but only half with temporal-lobe lesions showed jargon. In all these the damage was extensive.

Syntactical Errors and Telegram Style.—It seemed that "Style Nègre," as the French authors call it on account of its "pidgin" character, should be treated as a sub-group of disorders of grammatical structure.

Questioned about his speech trouble one patient (Case 45) said tersely: "Speaking. Not thinking." Case 32 said, "Juggler as a man do tricks"; and Case 26, "Juggler—two things mixed up." Examples of jumbled grammar are: "Lecture—well on gas anything to do with the Army one lectures," and (Case 32), "Gown is a thing on a morning and up on a bed." All these cases, too, had pronounced difficulty in word finding.

There were 19 patients showing some degree of agrammatism, including 2 whose expressive power was minimal. Only 3 had a fairly pure form of telegrammatic style, their propositions being otherwise correctly constructed. Their injuries were mainly frontal. In 3 patients there was a tendency towards telegrammatism with a more marked breakdown of syntax; 2 of these had only a mild degree of disturbed speech, articulation, and inflection; in 11 this was marked. In 11 patients some defective comprehension of language was associated with syntactical errors. Only 4, including those showing telegrammatism in its purer form, had little or no trouble with their spelling; these all had mainly frontal injuries.

Neurologically 14 had marked motor, and 13 marked sensory disturbances; 9 had visual field defects, with pronounced difficulty in writing; 10 had oral apraxia.

The fact that agrammatism may be associated with signs of disturbance both of the afferent and efferent systems, that is, with pre-rolandic as well as post-rolandic injury, is shown in Fig. 4.

Perseveration and Stammer.—In perseveration and stammer the characteristic feature is repetition.

As an example Case 46 may be quoted: "Mars. Mars, it's a, it's a, oh, is a god of war"; or the same patient defining "straw": "Dried 'ey; no it isn't; it is the wheat, ah . . . it's the thrust and—th . . . th . . . the, the thorn"; or defining "puddle": "Puddle? Water? Puddle is wa-water, gets, no, a w-water, dried, no, a dried, sticky, no, a puddle." Here we have

DISTURBANCE OF ARTICULATION, INFLECTION, SPEED

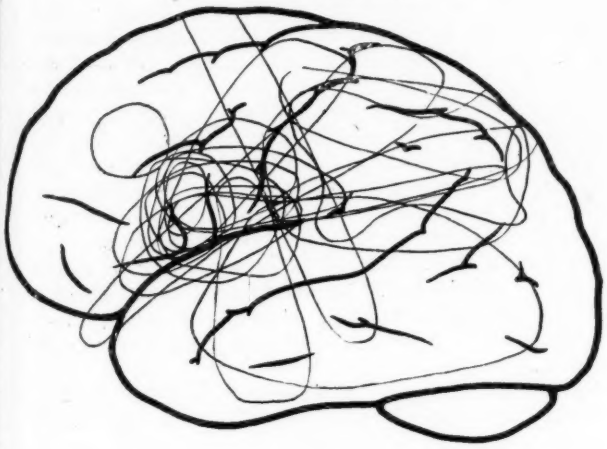


FIG. 2.—The wound contours converge to, and form the greatest density in, the foot of the precentral convolution and in the posterior end of the 3rd frontal convolution. There are only two exceptions (Cases 13 and 46) where there were parieto-rolandic lesions. Case 13 had a large gutter wound tearing the sagittal sinus, resulting in complete paralysis of the right upper limb and marked facial palsy ; one patient (Case 46) had a spinal fluid leakage and fungus cerebri with a similar neurological picture. It is therefore probable that in these two cases also the brain damage extended to the area where most of the wounds centred. (20 cases : Nos. 2, 5, 6, 7, 11, 13, 14, 21, 28, 32, 33, 35, 36, 37, 38, 40, 42, 44, 45, 46.)

PARAPHASIA

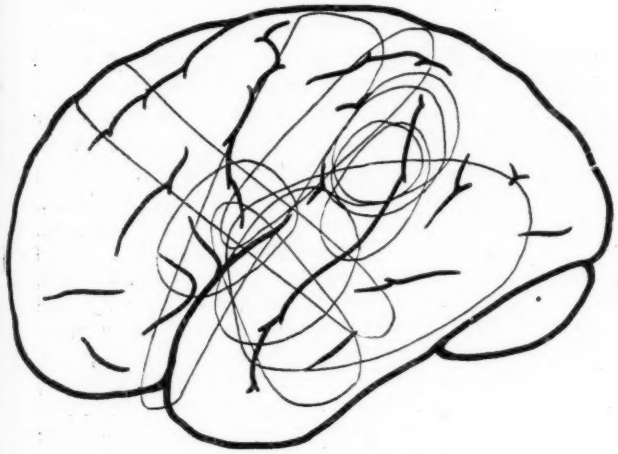


FIG. 3.—There are two areas with overlapping outlines. One (Group A) is fronto-temporal and is formed by widespread injuries ; it corresponds to patients with loss of articulation, inflection, and speed. The other (Group B) consists of relatively small wounds clustered round the hind end of the Sylvian fissure ; in this group there was no motor loss and no loss of articulation, etc., but marked field defects. (11 cases : Nos. 6, 10, 14, 15, 26, 30, 31, 38, 40, 42, 44.)

DISTURBANCE OF SYNTAX AND TELEGRAM STYLE

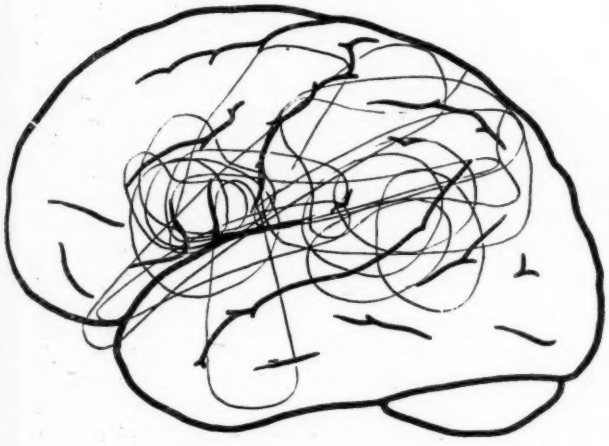


FIG. 4.—A fronto-temporal cluster of wounds producing telegram style and defects of tonality, rhythm, and speed. Another temporo-parietal cluster is from patients with gross disturbance of sentence and word patterns, and defective understanding, reading, and writing. (17 cases : Nos. 2, 3, 10, 11, 13, 14, 26, 30, 32, 33, 35, 36, 38, 41, 42, 44, 45.)

repetition of words, of syllables, and of initial sounds in a patient labouring to find, form, and pronounce the suitable word, being dissatisfied with the result, trying again, and at times finding himself thrown back to the starting-point. It is difficult to decide whether he is persevering in his task, or is the victim of involuntary perseveration, or both. Another example of distressing perseveration was Case 38 : " I can put my name down, K.S.P., and I can't put it down, police, and I thought I can't put it down, police, police, police, well it's hopeless."

Of the 14 cases in which perseveration was well developed, 2 had marked stammer but no other features to distinguish them from the rest of the group, which was characterized by predominantly " expressive " disturbances, and by marked difficulties in word finding and spelling. Twelve had the striking characteristic of severe sensori-motor hemiplegia ; 7 had marked hemianopic field defects, most of them mainly in the lower quadrant. The parietal and parieto-rolandic regions were conspicuously affected in all but 1 case (Fig. 5).

Auditory Incomprehension.—The study of comprehension of speech is more complex and less reliable than that of expression. We can observe an individual's response, but have no direct insight into how much he is taking in, and in what way. The severity of incomprehension was relatively less striking than the severity of expressive disorder in comparable groups of cases. Naturally it is easier to fit an object to a name than a name to an object. Although almost complete speechlessness was sometimes encountered, a similar degree of incomprehension was never observed, but all these cases were recovering or had recovered from the acute stage of injury, during which some of them may have had complete auditory incomprehension. The patients were rarely aware of " Speech-deafness " ; only one (Case 41) had the insight to say : " In a way, some of them, I can't hear them."

The ability to point to objects or pictures named by the examiner is the simplest test for the understanding of words. None of the 24 patients in this group made mistakes in performing it. A word given with a limited number of pictures exposed facilitates the correct association. These patients failed, however, to understand long, unexpected, and less common words, or to respond to oral commands. This failure was more noticeable when the task involved two or three concepts, such as " the hand " and " the mouth," or " to point " and " the window." Often it was necessary to slow down or repeat a command. Sometimes the patient would repeat it to himself before grasping its meaning and carrying it out, but this is, of course, only an exaggeration of the normal process in such situations.

Sentence-repetition cannot be uniformly tested since it involves variable factors : firstly it is possible to repeat word sounds without grasping their meaning ; secondly there is the factor of memory, inherent also in the execution of longer oral commands, and thirdly, there may be disturbance of the speech function concerned with the mobilization and formation of words.

Half the patients with disturbed auditory comprehension, including 3 of the most severe, had predominant difficulties of expression ; all 12 had very extensive wounds, manifested by gross loss of power and sensibility of the dominant hand (Fig. 6). Among our 20 patients with gross expressive disturbances (described under " Disturbances of articulation, inflection, and speed) only 3 had little or no auditory incomprehension, and of these one had a history of auditory incomprehension at an earlier stage, soon after wounding.

In the other 12 cases there was auditory incomprehension without difficulties of expression or weakness of the dominant hand. In these the lesion was in the temporo-parietal region. All had difficulty in word finding.

Disability to grasp visual symbols of speech (reading defects) was found in 18 of these 24 cases. Fifteen had gross hemianopic field defects.

Reading.—In silent reading the relevant mechanisms consist of the appreciation of visual symbols and of their association with meaningful words, which must be easy of access. In reading aloud patients with articulatory disturbances have the additional difficulty of expression. In the more severe type of disability the energy spent on integrating the word patterns leaves the patient with no reserve for appreciating their meaning (Pick, 1913).

On the other hand, the opposite difficulty was observed: " I get the meaning, but I can't read it out," explained Case 15 who had no disorder of articulation, inflection, or speed. One patient (Case 11) would easily find objects, when their names were given to him in print, and would execute written orders to some extent ; yet, when reading aloud he would take in the print at a glance, then shut his eyes and so apparently concentrate hard on trying to find the sound or kinæsthetic pattern for the word, the graphic symbol of which had conveyed to him its meaning. Another type of patient, who showed that he had grasped the meaning correctly, would nevertheless promptly translate the printed word incorrectly or by a synonym, for example, " for " instead of " of," " when " instead of " if," or " father " instead of " foster-parent."

Many patients, losing the mental track of the sentence and possibly handicapped by hemianopia, tend to omit words. On the other hand where the reader's appreciation of the meaning is guided by the context, his performance gains in efficiency and he may fill in by guessing what he fails to read.

Paraphasia and jargon complicate the picture of a reading disability (" paralexia ") ; as when a patient reads " gone back " for " look back," or " four enkerchief " for " your own education " (Case 14). Spelling the words aloud was sometimes found to help (Case 38). Extreme slowness in reading, without " paralexia," and in the absence of slowness of speech, was seen in Case 20, who took 45 seconds to read the twenty-word sentence, but without a mistake. This patient also took

PERSEVERATION AND STAMMER

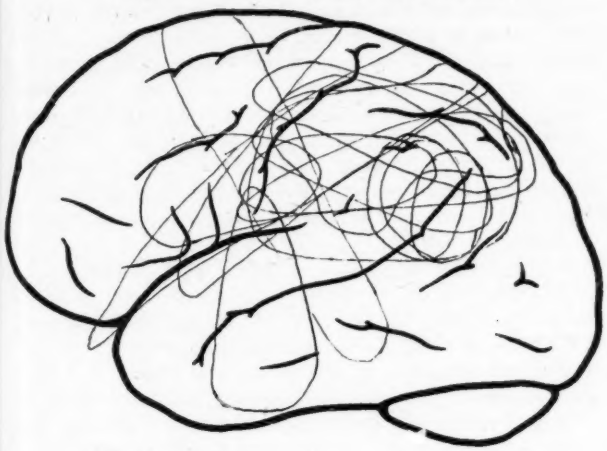


FIG. 5.—All lesions, with the possible exception of one, affect the parietal lobe. (14 cases: Nos. 1, 2, 3, 9, 13, 25, 26, 33, 35, 38, 40, 42, 44, 46.)

DISTURBANCE OF AUDITORY COMPREHENSION

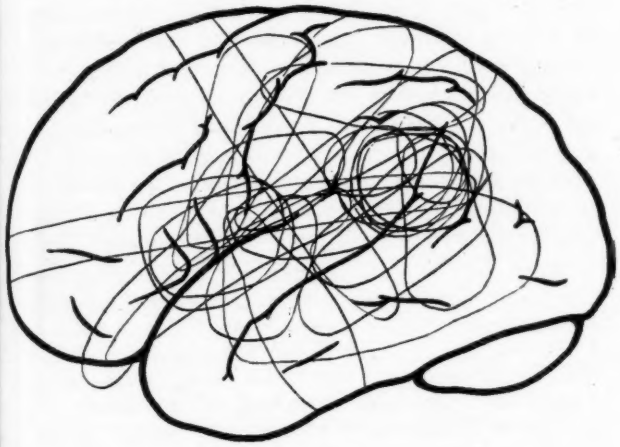


FIG. 6.—One cluster in the fronto-temporal region, of patients with associated gross expressive shortcomings. Another cluster, of smaller wounds, in the temporo-parietal region, corresponds to cases showing more isolated auditory incomprehension. (24 cases: Nos. 3, 6, 9, 10, 11, 12, 14, 15, 19, 20, 21, 23, 26, 29, 30, 31, 33, 35, 38, 40, 41, 42, 44, 46.)

DISTURBANCE OF VISUAL COMPREHENSION (READING)

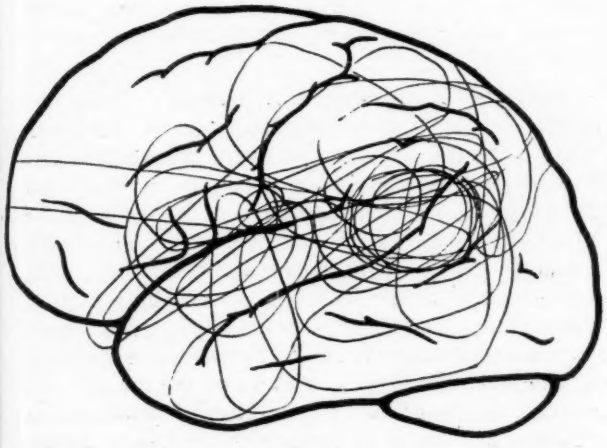


FIG. 7.—Greatest density of wounds in the temporo-parietal region. Three of the five wounds not extending into this area and probably purely fronto-temporal gave rise to no associated auditory incomprehension. (25 cases: Nos. 1, 2, 3, 6, 10, 11, 12, 14, 15, 19, 20, 21, 22, 23, 26, 27, 29, 30, 31, 32, 38, 39, 41, 42, 44.)

a long time before he, again correctly, identified the ten pictures of the test series when their names were given to him in print.

In some cases with dysarthria and paraphasia, however, reading aloud was better than spontaneous speech; here the visual word pattern served as an aid to word formation. Single numbers were read better than letters —a reflection on the fact that children usually learn numbers before learning the alphabet.

The 25 cases in this group had difficulty in word finding and in writing, as well as disturbed reading. Twenty showed considerable auditory incomprehension. Only 2 patients had no hemianopia. Sixteen had dysarthria, 4 severely. Motor loss was present in 11 cases, sensory loss in 15, field defects in 18 (Fig. 7).

Disturbance of Writing (Spelling).—Spontaneous writing was not tested, but only the grosser disturbances revealed by dictation.

Among our 46 cases there were only 7 (Fig. 8) who had no marked defect in spelling words such as " recommend," " business," " instruction," or " education." Of these, two (Cases 4 and 43) had small wounds, at the posterior superior end of the parietal lobe and at the tip of the temporal lobe respectively ; there was no significant disturbance of speech. The remaining 5 (28, 35, 36, 40, 45) with intact spelling had frontal lesions ; they had " expressive " shortcomings and difficulty in word finding, but two also had slight trouble in understanding the spoken word ; in these the wounds extended into the parietal and temporal lobes. One of these (Case 35), though spelling correctly, displayed the same slowness in writing as in speaking ; he took 7 minutes to write ten dictated words. In the other case (40) with a rolando-temporal lesion, spelling was better than vocal expression ; he was extremely slow. Another, with apparently intact handwriting (Case 28), was equally slow ; there remained 2 cases of normal spelling. A certain slowness, of course, has to be allowed for in a right-handed man whose right hand is paralysed so that he has to use his inexperienced left hand, but on the whole retardation was too gross to be accounted for by this handicap alone.

Nineteen out of these 39 bad spellers were selected on account of their outstanding defect. The spelling of a word was made easier for them, after they had failed, by the examiner's spelling out each letter. Six were unable even to write their own names, the easiest writing performance except for writing numbers. Nine had some difficulty even in copying letters and words. Case 15, an intelligent officer in perfect general health, would display a slight tendency towards mirror-writing in copying, using something like a Greek " μ " instead of a " y," " β " for " b," or the number 8 as a substitute for various letters. He would also write down four incoherent vowels, " a, i, e, u " in response to the dictated number five. This happened 15 days after he was wounded ; 4 months later these particular features had disappeared but he was still dysgraphic. Another officer (Case 22), having a left parietal wound with unawareness of the right arm, was not only unable to copy letters, numbers, and simple shapes, but also failed in the simplest arithmetic and the construction of Kohs' block patterns ; he could not use his intact left hand and arm for waving and showing the movement of using a key, either spontaneously or by imitation. While understanding the command, he somewhat aggressively expressed disappointment with his failure. Referring to his inability to write with his left hand and refusing to admit his obvious apraxia he said : " I can't write at all because of my left hand, you see I'm right-handed, I've never been able to use my left hand," an excuse not encountered in any other patient.

Eighteen out of 19 had difficulty with reading ; 15 a marked degree of hemianopia ; 12 were poor in handling Kohs' blocks, and 10 in handling figures ; 15 had some trouble in understanding speech ; 9 disorders of articulation, inflection, and speed ; 9 had marked motor, and 9 sensory loss in the dominant hand.

Fig. 9 shows the importance of the parietal lobe for writing ; only 5 out of 19 cases had fronto-temporal lesions, but with extensive loss of brain substance.

Disturbed Ability to Construct.—Kohs' blocks test, for examining abstract thinking by calling upon the ability to analyze and handle relationships of space and colour was given as a non-verbal test, as such ability is often affected together with speech. Only gross failure in the absence of gross dementia, as assessed by the patient's general behaviour, was considered significant. Patients were given only the first five very simple patterns. No attempt was made to establish an upper performance level for those who undoubtedly would have done better.

There were 18 patients who, by their slowness or complete failure in some patterns, showed a performance level corresponding to a mental age from 12 down to 7 years, or an intelligence quotient ranging from 87 per cent. down to 49 per cent. All these, as one would expect, had abnormal difficulties in calculation and spelling, in addition to impaired word finding ; 15 had definite reading disturbance, 13 impairment of auditory comprehension, 7 disorders of articulation, inflection, and speed. Fourteen had visual field defects, 13 sensory defects, and 11 loss of motor power of the dominant hand. All except one had wounds impinging on the parietal lobe, most of them in its posterior-inferior part (Fig. 10).

Disturbances in Simple Arithmetic.—These are related to aphasic shortcomings in at least two ways ; firstly in that numbers themselves are symbols for concepts, and secondly in that their handling requires the integrity of general mental processes such as memory, visual and spatial imagery, and thinking in abstract categories. The performances may either be considerably slowed down (though yielding a correct result) or the result may be incorrect, or both. As slowness of expression is a natural handicap in presenting the results, this in itself was not made a criterion of failure, except where it was out of proportion to the speech defect.

NO SPELLING DEFECT

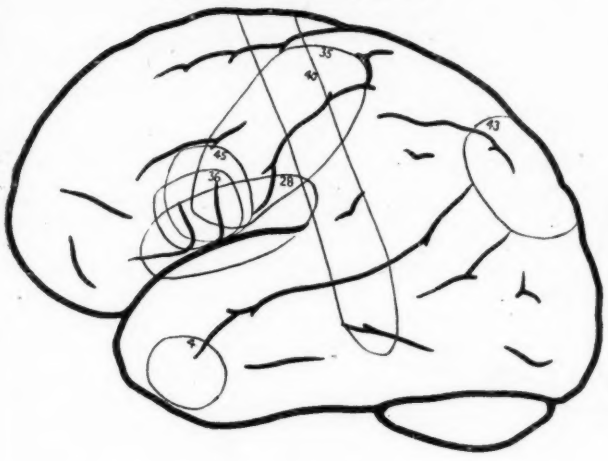


FIG. 8.—Four wounds affecting Broca's area. Two cases outside the greater speech area. One exterior temporo-rolandic wound. (7 cases: Nos. 4, 28, 35, 36, 40, 43, 45.)

MARKED SPELLING DEFECTS

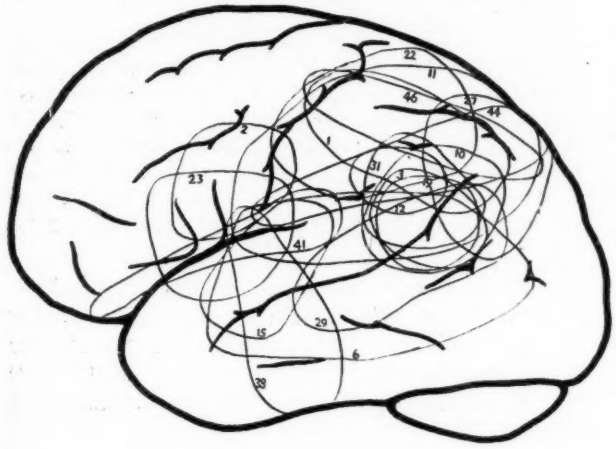


FIG. 9.—Note the predominant involvement of the parietal lobe. (18 cases: Nos. 1, 2, 3, 6, 10, 11, 12, 15, 19, 22, 23, 27, 29, 31, 38, 41, 44, 46.)

INABILITY TO CONSTRUCT
(KOHS' BLOCKS TEST)

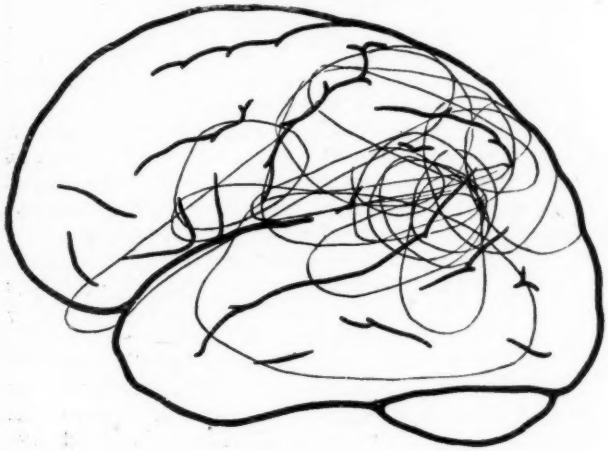


FIG. 10.—Note the predominant involvement of the parietal lobe. (18 cases: Nos. 2, 3, 6, 9, 11, 12, 16, 19, 20, 22, 27, 30, 31, 32, 42, 43, 44, 46.)

RAVEN'S MATRICES

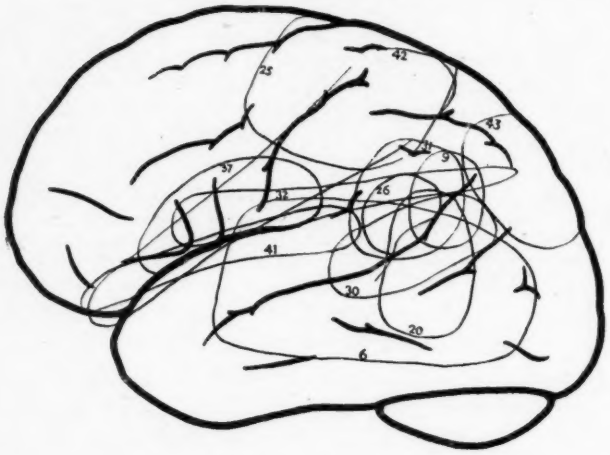


FIG. 11.—Wounds of patients whose score was in the under-25 per cent. group; some of them relatively small; most of them in the temporo-parietal region. (12 cases: Nos. 6, 9, 20, 25, 26, 30, 31, 32, 37, 41, 42, 43.)

Moreover when the patient is labouring with the task of relating figures to each other, his expression may suffer. The converse, when the difficulty in saying and finding words interferes with the process of calculating, is found even more often.

Some more intelligent patients were able to give the results in their own imperfect but correct way, by tapping or by saying: "Five-one" instead of "Fifty-one." In performing written sums characteristic mistakes were found, such as the failure to carry over or to treat a number according to its place in the decimal system. This may well be due to inability to keep in mind spatial and part-whole relationships. It also contains an element of perseveration. There were in all 24 cases, including the 18 already mentioned in the previous section.

Apraxia and Agnosia.—There was only one definite case of apraxia (Case 22), which has already been mentioned in association with a writing disability. No obvious case of pure visual agnosia was found.

Impairment of General Intelligence and Categorical or Abstract Thinking.—Twenty unselected cases were given Raven's Matrices, an intelligence test which, though apparently non-verbal, seems to require some internal verbalization.

Table

	Percentile groups									
	Under	5	10	25	50	75	90	95
No. of cases (total 20)	..	7	2	3	4	3	1	0
Intelligence	..	Below			Average		Above	
No of cases. (total 20)	..	12			7		1	

The Table shows that 35 per cent. (7 out of 20) were in the lowest percentile group, and the majority of cases, i.e., 12 (60 per cent.), below average. Only 4 or 5 out of the 12 had extensive brain wounds.

Two and a half months after being wounded one patient (Case 43) had no obvious remaining aphasia but scored badly with Kohs' blocks and the serial seven test. A printer and compositor in civilian life, he must have been of at least average intelligence. His wound was an upper parietal one. The rest of the cases with low intelligence scores had wounds and aphasic disturbances mainly of the parietal and parieto-temporal type (Fig. 11).

Left-Handers with Right Hemisphere Wounds.—The two cases encountered (17 and 34) were similar in most aspects. Left-handed without any such family history, they had both been taught to write with their left hand and used it as the dominant hand in their daily lives.

Case 17, aged 26, was a corporal, in civil life a clerk in a chemist's shop; Case 34, aged 25, a regular trooper. Neither had stammered in childhood. Case 17 had received a shallow laceration midway across the right rolandic area, probably extending into the temporal lobe, followed by unconsciousness (post traumatic amnesia for three weeks). He had never been definitely aphasic. When seen six months after being wounded he had a moderate left facial weakness, complete spastic paralysis of the left hand with complete loss of postural sense and astereognosis, and slight left upper and moderate left lower quadrantic homonymous hemianopia. He had no oral apraxia, and his spontaneous speech and his reading abilities were perfectly normal; but his difficulty in learning to write with his right hand was far in excess of right-handed persons who have to change over to the left hand. He wrote very slowly and in clumsy block letters which tended to increase in size towards the end of the words, and he spelt wrongly nine- and ten-letter words ("reccomend"; "copngeous" for courageous). Moreover he was unable to carry out the serial seven test; he produced "83, 79, 72," and gave

up after a struggle lasting two minutes. He was tested with Kohs' blocks two months after his injury, when he was found unable to do even the simplest pattern.

Case 34 had a more extensive wound, three finger-breadths wide across the upper right fronto-rolando-parietal area, that is, away from the speech area. His injury had also resulted in complete paralysis of his left hand, with moderate loss of postural sense and fairly marked astereognosis but no hemianopia. When seen two and a half months after being wounded his expression and understanding of the spoken word, as well as his reading, were normal. But he, too, had disproportionate difficulty in learning to write with his right hand; his letters were too large and unwieldy, and some words of over seven letters were wrongly spelt. Moreover he made mistakes in carrying over when doing a sum; but made only one error in the serial seven test, for which he took eighty seconds. He was unable to perform one of the first five Kohs' blocks patterns.

Discussion of "Nominal" ("Amnesic") Aphasia.—The term "nominal" aphasia is usually applied to a patient's failure to give a name to a thing. The term is derived from Head's classification, but its use is an over-simplification and distortion of the author's definition. This comprised not only the "loss of power to employ names," but also the loss of "*comprehension* of the nominal value of words *and other symbols*," that is, not only the inability to fit a name to an object and an object to a name, but also a defective appreciation of written language and of numbers. The term "amnesic" aphasia first appeared in the French, then in the German and American literature to describe disturbed memory for words. "Logically," Weisenburg (1935) said, referring to patients with difficulty in evoking words as names for objects, "patients of this type belonged to the predominantly expressive group. Psychologically, however, their disorder was so different in nature that they could not well be classified with that group. Neither did they belong to the predominantly receptive group, for their understanding remained always relatively superior." A fourth group (the third was the mixed expressive-receptive) was, therefore, "created" and called amnesic. This term brings us back to Broca's "verbal amnesia," which included all speech disturbances that were not "aphemia," the latter being due to lesions of the third frontal convolution. Goldstein (1932) speaks of "central" aphasia, a term almost synonymous with "nominal" aphasia.

"Amnesic" or "nominal" aphasia in the current, popular sense of the word was found in all our patients according to their main shortcomings in either expression or understanding. Although it often seemed to be the predominant feature, it was never found as an isolated phenomenon. Nominal aphasia, being an integral feature of any type of aphasia, is therefore the least helpful finding for localizing a lesion within the speech area.

There were, however, two patients (Cases 16 and 43), right-handers with left hemisphere lesions both in the upper parietal region, who at the time of examination—two and a half and ten months respectively after being wounded—showed no signs of nominal or other type of disordered speech. Case 16 had also a right parietal intracerebral clot. These cases were included in our series because they displayed defective calculation, construction, and spelling, with a residual weakness of the right hand and field defects. Case 43 was reported to have shown earlier a "nominal aphasia and alexia."

General Discussion

Wilson (1920) and Weisenburg (1935) objected to the choice of brain injuries for this type of inquiry because of the generalized effects of concussion and of other widespread or multiple damage. The advantage of studying traumatic cases, however, is that they present circumscribed lesions and can be examined during convalescence. There is a less generalized disturbance of brain function than in cases with raised intracranial pressure or vascular disease.

Although subordinate to the effects of focal brain injury, several other factors seemed to influence the clinical picture. These may be divided into (*a*) personal and pretraumatic factors, and (*b*) those due to trauma.

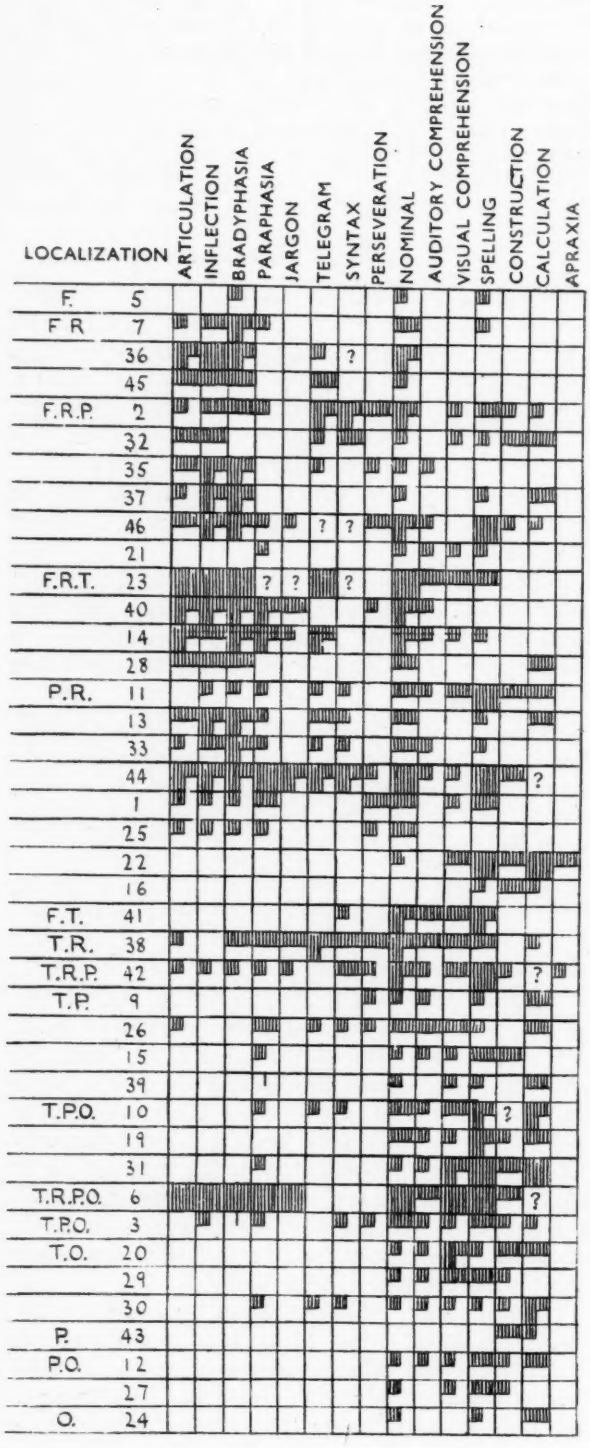
Personal and Pretraumatic Factors.—These include heredity, mental age, the preponderance of a visual or acoustic type of memory, the level of education, trends of personality, and pre-existing speech disturbances.

Factors due to Trauma.—These may themselves be subdivided into general and local factors.

General Factors

(*a*) *The Time Factor.*—The more recent the injury the more severe and global were the aphasic features. This was probably due to traumatic effect on large areas surrounding the lesion, these being put out of action by "concussion" or œdema. In a normally healing wound recovery from aphasia was rapid within the first month or two. Thence the speech disorder maintained its characteristic pattern, but usually decreased in severity. The pathology and extent of the lesion determined the degree of recovery.

(*b*) *The Bulk of the Tissue Destroyed.*—The ultimate clinical effect of a large injury and the immediate effect of a small injury are comparable. Small wounds bordering on, but not directly affecting the speech area (Cases 16, 43) may cause



little disturbance once the adjacent regions concerned with speech have recovered from the transient initial damage.

In order to separate the effects of massive destruction of brain matter verging on the classical "speech centres," from lesions around the Sylvian fissure, we should distinguish between "global" and "total" aphasia, that is, between the range of abnormal manifestations, and their severity or degree. A patient with "global" or "mixed" aphasia is one who shows some disorder which may be mild, but affects all or most aspects of speech; a "total" aphasic is one whose global aphasia is of such a degree that he has lost almost all normal means of social intercourse. Such a patient will, in fact, be demented as well as speechless.

Although it was difficult to assess the volume of brain tissue lost or permanently put out of action, the 13 cases with very large wounds did in fact show the greatest collection of individual disorders of speech (1, 2, 6, 11, 13, 23, 26, 32, 38, 40, 42, 44, 46).

A very large wound bordering on, but not directly affecting the left perisylvian area may cause moderate global aphasia (44, 46). The mere volume of dominant hemisphere tissue destroyed, irrespective of its localization, will, therefore, influence the degree of speech and intelligence less, but local factors dominate in determining the type of aphasia.

LOCAL FACTORS.—Fig. 12 has been compiled from the individual charts of each case. It is supplementary to, and a summary of, the cumulative charts. In this table the localization of each brain lesion is correlated with all the symptoms displayed by the case. The list of cases starts with frontal lesions (F), followed by lesions situated further backward along the Sylvian fissure, first above it (F.R.), then including the temporal lobe (F.R.T.), etc. The severity of each feature is expressed in quarter squares, according to the degree of disturbance, as plotted from 2 (slight) to 5 (extreme) on the individual charts (Fig. 1). "General factors," in particular the bulk of tissue destroyed, have had a considerable influence in shaping the aspect of the table, e.g., in Case 6 who had a lesion affecting T.R.P.O. (Temporo-rolando-parieto-occipital).

FIG. 12.—Summary of results shown in "cumulative charts." F=frontal; F.R.=fronto-rolandic; F.R.P.=fronto-rolando-parietal; F.R.T.=fronto-rolando-temporal; P.R.=parieto-rolandic; F.T.=fronto-temporal; T.R.=temporo-rolandic; T.R.P.=temporo-rolando-parietal; T.P.=temporo-parietal; T.P.O.=temporo-parieto-occipital; T.O.=temporo-occipital; P.=parietal; P.O.=parieto-occipital; O.=occipital.

Three outstanding points may be noted :

1. More than one aspect of speech is affected in each case.

2. " Nominal " aphasia is present in almost all cases, wherever the wound.

3. Disorders to the left of the chart give place to those on the right as the site of wounding becomes more posterior.

In a more detailed study of the cases the following points on localization emerge :

(*a*) *Frontal Lesions.*—Wounds affecting the lower part of the precentral area produce disturbances in articulation, inflection, and speed. Poverty of speech, laziness, and telegrammatic style are common. It is irrelevant whether such terms as " anarthria " (Marie), " motor " (Wernicke), " verbal " (Head), " expressive " (Pick), or " Broca's " aphasia are used for their designation. Word finding is also impaired in these cases, and there may be repercussions on other aspects of speech.

(*b*) *Temporal Lesions.*—The more a lesion encroaches on the temporal lobe, the more impaired is the auditory control of what the patient says and his understanding of word sounds. Auditory control implies that auditory schemata regulate the speech act, and influence the shape of words and phrases supplied from, or identified by memory.

The nearer to the frontal lobe a temporal lesion is situated, the more will the disturbed performance be tinged with " frontal " characteristics. Telegrammatic style will be prominent, together with other syntactical shortcomings. Paraphasia and jargon are the outcome of most lesions of the first temporal convolution ; but when the former are present the parietal lobe is also usually affected.

The further back the lesion in the first temporal convolution, the greater is the disturbance of reading and writing, in addition to auditory incomprehension.

(*c*) *Parietal Lesions.*—All aspects of speech related to orientation in space are affected in parietal lesions. Writing and spelling, being a translation of words into symbols of shape and space will be grossly impaired ; also reading and calculating, and the ability to construct. Perseveration with or without stammer is common, especially with large wounds, and word schemata are particularly difficult of access. In fronto-parietal lesions there appears to be a characteristic hold-up between the acts of recalling a word, and translating it into a sound and kinæsthetic pattern, ready for the final vocal delivery. The more widespread the lesion, and the further back and up along the slant of the Sylvian fissure, the more pronounced is the patient's intellectual loss.

One will agree with Jackson (1932), Pick (1913), Head (1926), and Goldstein (1932, 1942), that an aphasic is essentially an individual struggling to readapt himself to the havoc wrought in those parts of the dominant hemisphere which surround the Sylvian fissure. The abnormal features of such a patient elude precise terminology. Dysarthria in its most severe form may be indistinguishable from paraphasia ; paraphasia in its highest degree may be called jargon. In the telegrammatic type syntactical errors are allied to purely expressive disorders ; on the other hand auditory incomprehension may be responsible for some manifestations of agrammatism. Perseveration plays its part in both " expressive " and " receptive " disturbances, efferent and afferent impulses interacting to impede one another.

There seem to be two allied reasons why aphasia should be mixed—its composition varying with each individual : one is the close functional interconnexion of cortical areas whose damage leads to disorganization of speech ; the other lies in the very nature and evolution of speech, which is not merely a system of symbols to convey ideas and emotions, but has been primarily developed as an instrument for man's action and intercourse in society. As such it is firstly an aid to the tactile organs, mainly the dominant hand. We speak in order to attract and repulse, to get things, and get things done for us. Secondly, an object known by its name, a relationship grasped through a phrase, help with their perception. Percepts are differentiated and intensified by words which facilitate memory processes. Thus the interplay of action, perception, and memory is enhanced by speech, and diminished by its disorders. This relationship of language to the main functions of the central nervous system is mirrored in the topography of the speech area in the cerebral cortex.

In trying to classify pathological phenomena of speech we have first to distinguish and then to correlate three different approaches to the aphasic patient, each approach implying a different set of data and terms. First, we describe the recorded products of disturbed speech in terms of phonetics (e.g., dysarthria) and linguistics (e.g., paraphasia or agrammatism). Secondly, we interpret the act of speaking in physiological and psychological terms (e.g., motor, or amnesic). Thirdly, we have a verifiable lesion in the brain which is qualified anatomically. It is the correlation of these three sets of terms which so complicates the final classification of aphasia, and only our anatomical findings are strictly capable of isolation, definition, and

measurement. We are reminded of Goldstein's (1942) warning: "We must first know *what* we have to localize." Should we then agree with Head (1926) that it is "of no use trying to localize the position of an unknown function on the surface of the brain" and with Weisenburg that "localization of language and its disturbances is impossible"? Since none of our patients with aphasia was free from difficulties in word finding, can we accept Marie's distinction into "anarthria," a purely physical phenomenon, and "aphasia," a purely mental one? Or, on the other hand, should we adopt Kinnier Wilson's (1920) attitude (based on Liepmann (1908)) that "motor aphasia is but a part of apraxia and sensory aphasia of agnosia," knowing that none of these four qualifications covers the facts observed by us? In the light of our findings such resignation seems not altogether justified.

Despite the assumption that "symbolic formulation and expression are integrated on a level superior to that of motion and are of a higher order than sight and hearing" (Head, 1926) we believe that disorders of speech are closely allied to the known functions of the cerebral cortex. Head also stated that "there were no such things as 'types' of aphasia," but went on to set up his four loose groups of "verbal," "nominal," "syntactical," and "semantic" aphasia, linguistic terms which have not been widely accepted as they are neither self-explanatory nor practical nor natural. Yet aphasic manifestations tend to fall into groups according to the predominant features. Weisenburg's (1935) terminology (based on Pick's) distinguishes, in functional terms, between "expressive," "receptive," and "amnesic" types. Although this is convenient, it does as little justice to the majority of cases as did the old distinction between "motor" and "sensory" aphasia, and our findings do not justify the separation of an "amnesic" group.

Thus, all attempts to classify aphasia according to the type of functional disorder have proved disappointing. Yet a practical classification is required to indicate the part of the brain affected in any aphasic patient. "Diagram-making" has been rightly scorned by Head, and we are well advised not to regard the cortex as a mosaic. But our findings imply association of a certain mixture of symptoms with some approximate area in the brain. This area is roughly predictable after careful estimation of the patient's responses to a wide range of psychological tests, and grading of the results in order of their predominance. Instead of the unsatisfactory classifications in functional terms, we might then refer to frontal, fronto-temporal, temporo-parietal, and fronto-parietal types of aphasia. Although we cannot achieve the relative accuracy of localization which obtains at lower levels of cerebral integration, we feel justified in using those broad and simple anatomical terms.

Summary

1. In an attempt to elucidate and simplify the problems of terminology, classification, and cerebral localization of aphasia, 46 war casualties with penetrating missile wounds of the dominant hemisphere and some disorder related to speech function were examined.

2. These men were subjected to 20 standardized tests, most of them short and simple, including abbreviated forms of vocabulary, Kohs' blocks, and Raven's matrices tests.

3. The results were plotted on graphs, by giving "marks" ranging from 0 to 5, in order to chart the relative degree of disturbance in each aspect of speech.

4. Cumulative diagrams representing the surface of the dominant hemisphere were used, on which were mapped out, in their approximate size and site, the brain wounds of each patient displaying any particular aphasic feature. The area of greatest density produced by these superimposed wound contours was thus interpreted as the area most commonly affected in patients suffering from that particular aspect of aphasia.

5. The analysis of the findings confirmed the mixed nature of most aphasic disorders, their ill-defined and transitional character, and their relative dependence on personal and other pretraumatic factors.

6. In all cases with true aphasia there was difficulty in word finding ("nominal" aphasia), regardless of the site of the lesion within the "speech area." This essential feature is, therefore, considered the least valuable for localization. Spelling was likewise affected in all but 7 cases.

7. Follow-up studies showed that the earlier pattern of the speech disorder persists, though great improvement in the degree of disability occurs.

8. The grading of the severity and the relative prominence of each feature was considered important, but no rigid dichotomy into afferent and efferent types of disorder could be established.

9. Frontal lesions tended to impair most the speaker's initiative, the speed of his enunciation, the articulation of his words, and the inflection of his voice.

10. Temporal lesions hampered the understanding of spoken language, both of what the patient was saying and what was said to him. The structure

and interpretation of words and sentences suffered (paraphasia, jargon, and agrammatism) by the loss of auditory control on a high level.

11. Posterior-temporal and temporo-parietal lesions interfered mainly with the interpretation of visual symbols of speech (reading and writing).

12. Parietal lesions in particular caused a disturbance of all those faculties related to orientation in space and appreciation of shape; the pattern of the word or proposition to be said, read, or written became distorted. Stammer and perseveration were also common.

13. Lesions of the posterior part of the Sylvian area were the most deleterious to the more highly organized intellectual aspects of speech function.

14. The bulk of brain tissue destroyed was proportional to the severity and extent of the disorder involving both speech and intelligence.

15. Two left-handed patients with trans-rolandic right hemisphere wounds had difficulty not with speaking, but with writing, counting, and constructing.

16. The application of a set of tests and a graph for grading of severity, as outlined above, may make it possible to pick out the salient features of any given case of aphasia in about one hour. The judicious analysis of such a mixture of signs will then outline the responsible lesion in the various combinations of frontal, temporal, and parietal areas. For the sake of expediency it is therefore suggested that cases of aphasia should be classified in anatomical and not in functional terms.

I am greatly indebted to Professor Sir Hugh Cairns and to Dr. W. Ritchie Russell for permission to examine the patients under their care, and for their helpful comments; and to Dr. Eric Guttmann for his suggestions regarding the tests.

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